VOL. 36 JANUARY 1960 NO. 1

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

CHARLES E. KOSSMANN

ALBERT C. SHERWIN

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INFLUENZA AND UPPER RESPIRATORY INFECTIONS

Transcription of a Panel Meeting

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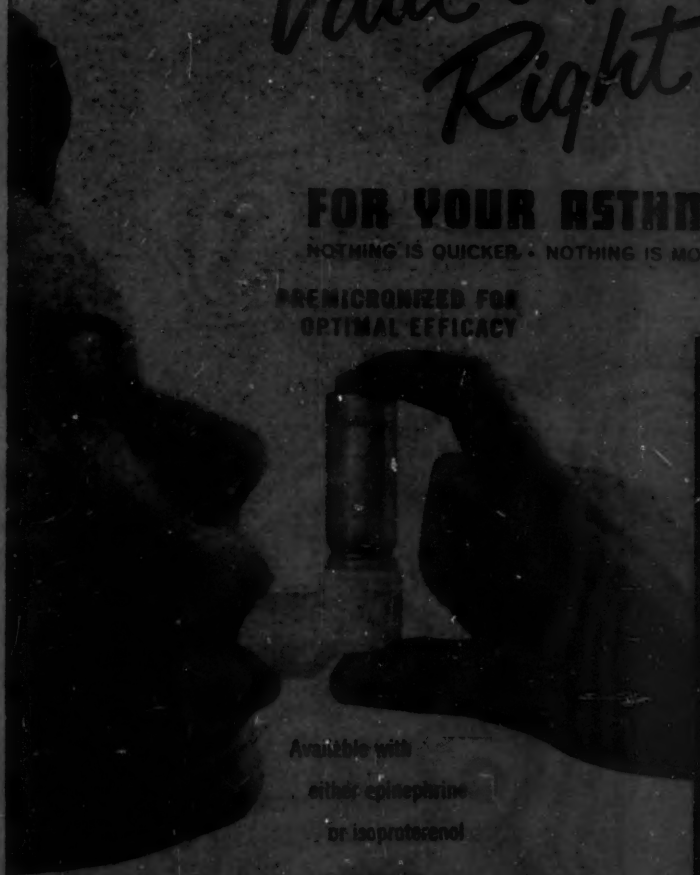

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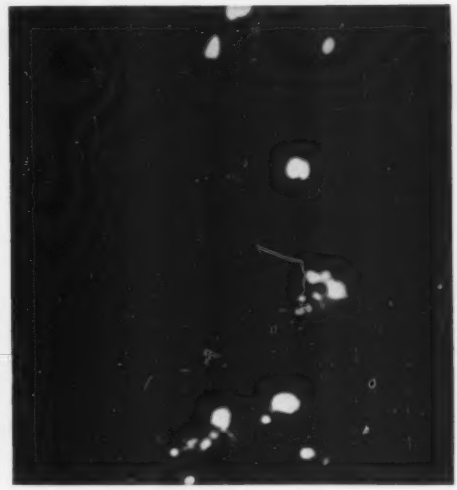

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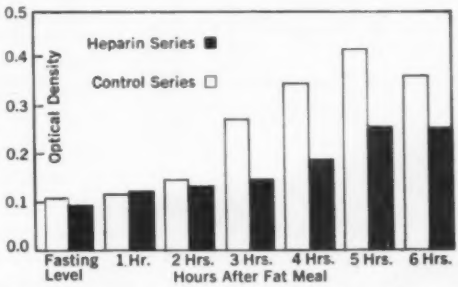
1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



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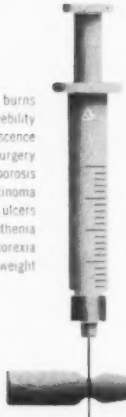

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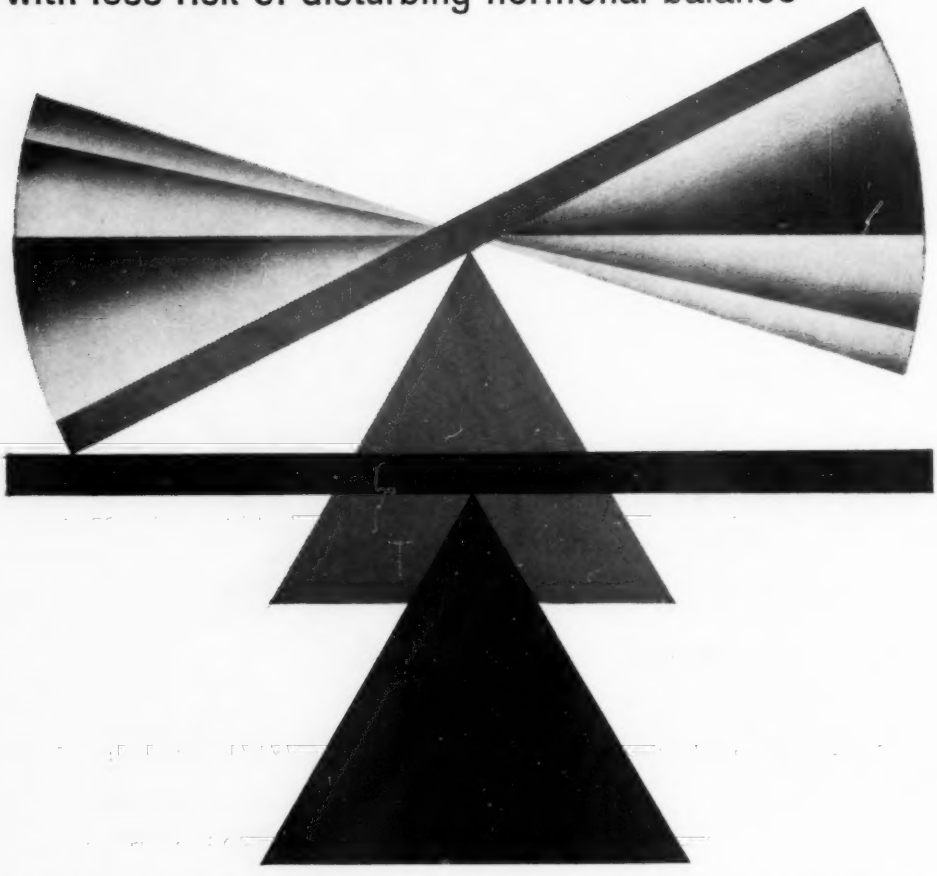

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1. Kuzell, W. C., and others.: Arch. Int. Med. 92:646, 1953. 2. Wolfson, W. Q.: J. Michigan M. Soc. 54:323, 1955. 3. Strandberg, B.: Brit. J. Phys. Med. 19:9, 1956. 4. Platt, W. D., Jr., and Steinberg, I. H.: New England J. Med. 256:823 (May 2) 1957.

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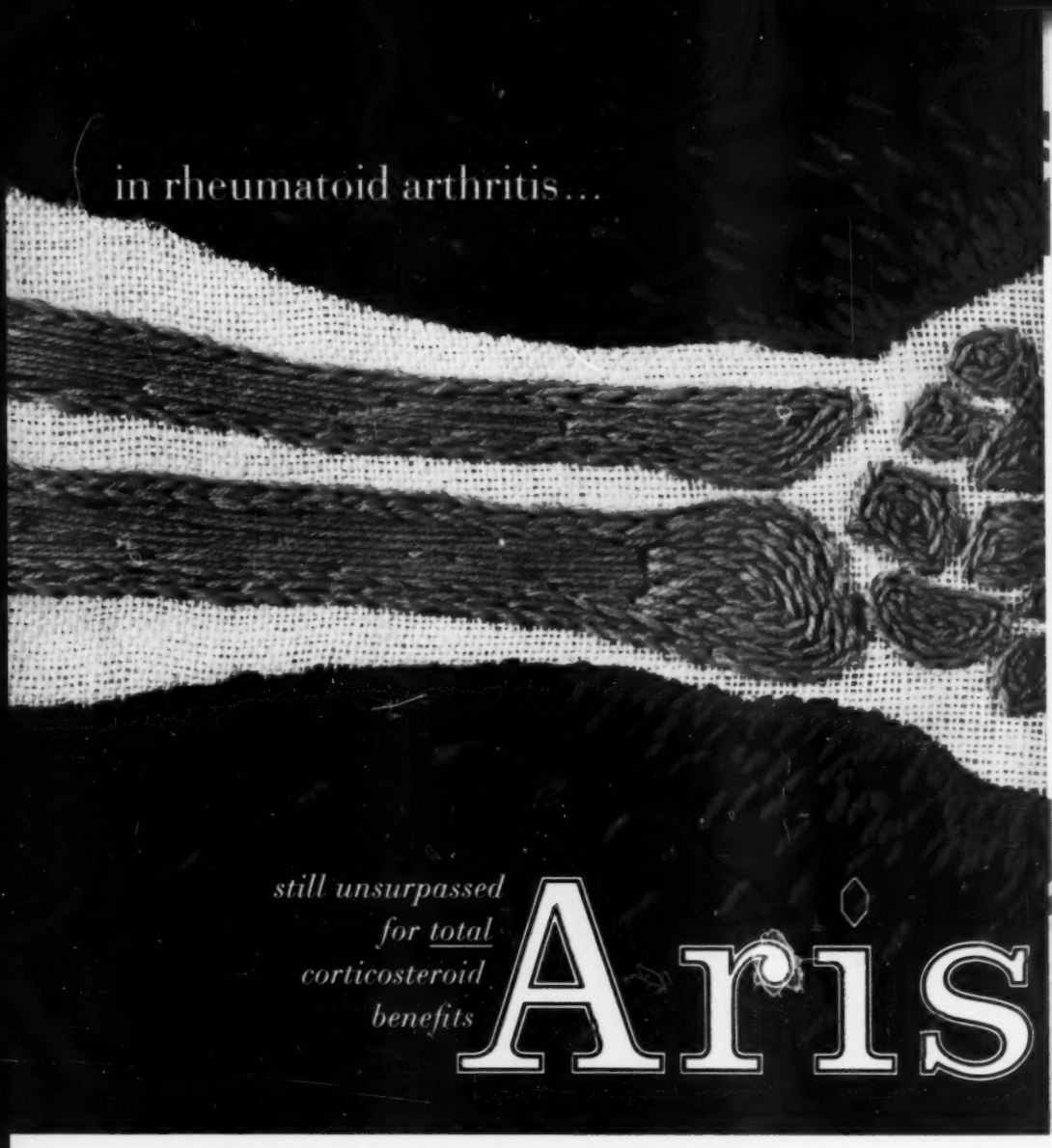

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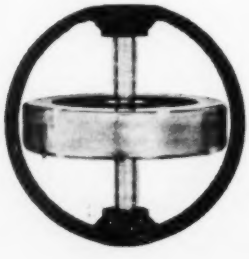

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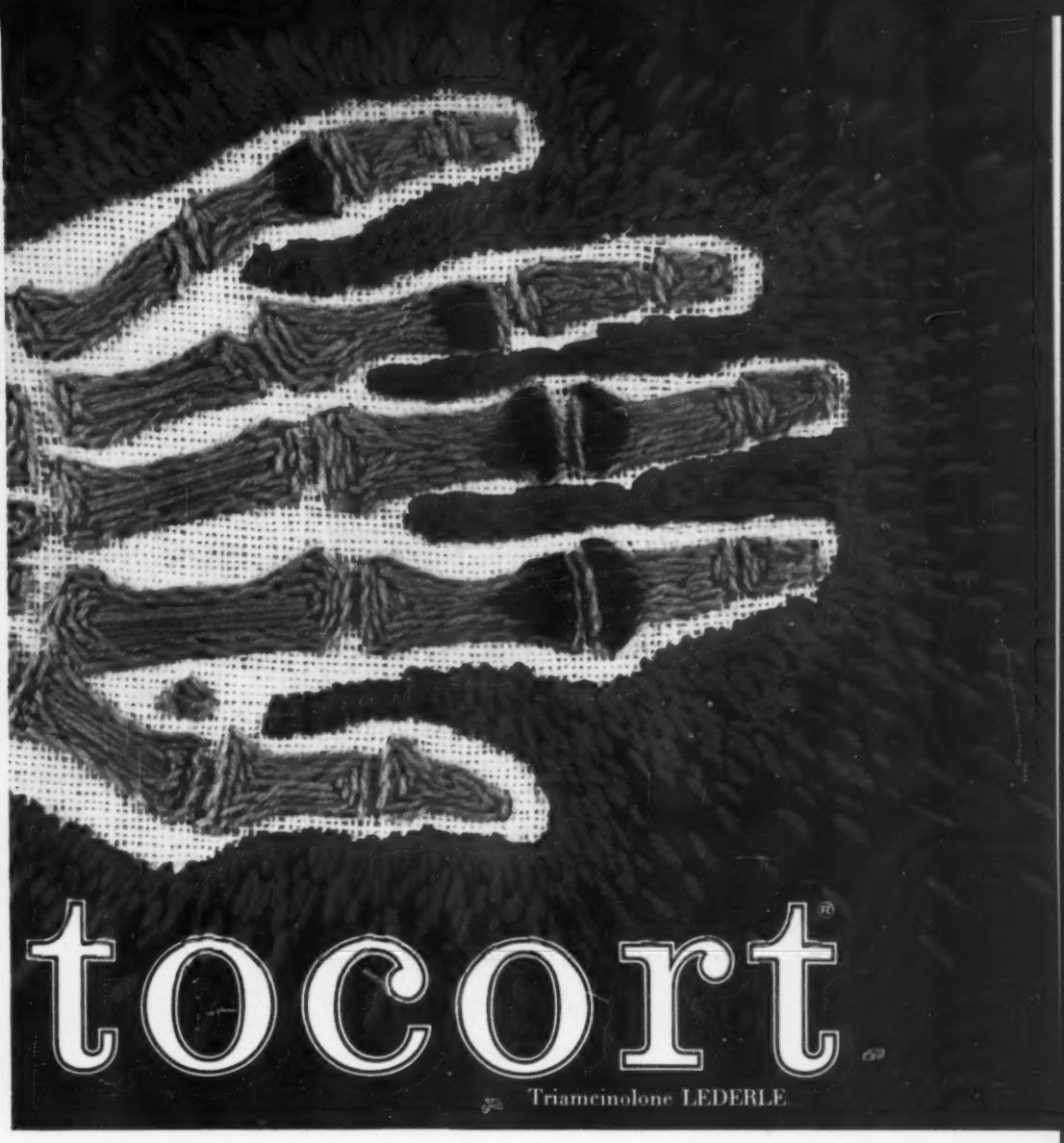

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*Green, J. B., & Steelman, H. F.: Epileptic Seizures, Baltimore, Williams & Wilkins Company, 1956, p. 136.

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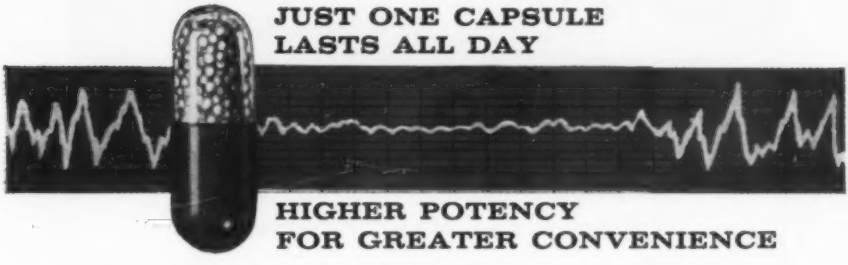

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*Miller, J.B., et al.: Ann. Allergy, 12:611, Sept.-Oct., 1954.

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SECOND SERIES JANUARY 1960 VOL. 36, NO. 1

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CONTENTS

Some Clinical Aspects of the Bioelectrics and Electrochemistry of Myocardium 3
Charles E. Kossmann

Influenza and Upper Respiratory Infections 22
Transcription of a Panel Meeting
Walsh McDermott, Edwin D. Kilbourne, David E. Rogers and Harry M. Rose

Musical Creativeness and Emotional Disturbance . . 55
Albert C. Sherwin

Research or Stagnation 69
George K. Smelser

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 36, NO. 1 JANUARY 1960

SOME CLINICAL ASPECTS OF THE BIOELECTRICS AND ELECTROCHEMISTRY OF MYOCARDIUM*

CHARLES E. KOSSMANN

Associate Professor of Medicine
New York University College of Medicine, New York, N. Y.

IT IS OFTEN stated that the Physiology of today is the Medicine of tomorrow. Mine is the prophetic task of bringing to a clinical level what is known about the transmembrane potential and its electrolytic origin. The adjective prophetic is used advisedly because, between the Physiology of today and the Medicine of tomorrow, there is obviously a time parameter which has not yet elapsed. However, my talk will not be one entirely of prophesy, because if it be true that the Physiology of today is the Medicine of tomorrow, it is also true that the Medicine of today is the Physiology of tomorrow. This may make it possible for me to attire some old medical facts in new and shining physiological raiment and perhaps strip a few clinical fancies of their tattered and long since outmoded cloaks of ignorance.

* Presented at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, November 25, 1958. Manuscript received January 1959.

From the Department of Medicine, New York University College of Medicine, the Electrocardiographic Laboratory of the Third (N.Y.U.) Medical Division of Bellevue Hospital, and the Cardiovascular Service and Heart Station, Lenox Hill Hospital, New York, N. Y.

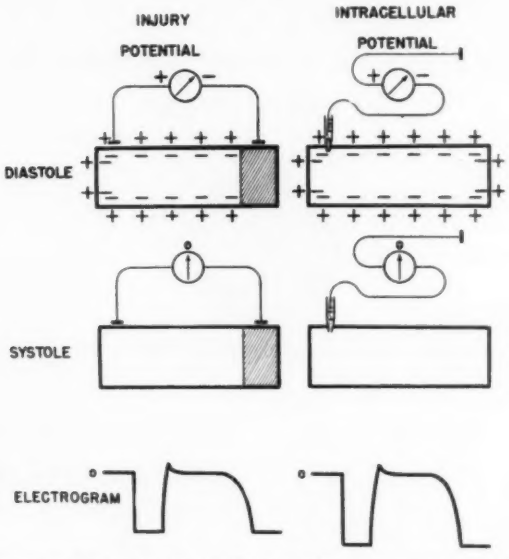

Figure 1. Diagram to illustrate the similarity of electrograms obtained by recording the injury potential (shaded area of cell is injured, e.g., depolarized) and the intracellular potential. The second electrode, when recording the latter, is assumed to be in a surrounding conducting medium distant from the cell. The smaller magnitude of the injury electrogram is the result of loss of potential by short circuit through the surrounding medium. (From Kossmann, in *Advances in Electrocardiography*[4]. This Figure, together with Figures 2 and 6, reproduced by permission of the author and the publisher, Grune & Stratton, Inc., New York.)

Clinical Aspects of the Membrane Action Potential

That the action potential of the myocardial cell of animals had the approximate monophasic form shown earlier this evening* was known since the time of Matteucci[1]. In man, a reasonable facsimile has been obtained by means of the intracardiac catheter-electrode when this electrode is pressed against the endocardium. Pressure or touch potentials of this kind have been obtained in all four chambers of the human heart[2]. The origin of these touch potentials, consisting as it does of excitation block[3] at the electrode, is somewhat different than is the case for the monophasic action potential of the older physiologists. Their records were obtained by pairing a healthy end of a muscle strip through a galvanometer to an injured end. The approximate experiment, reduced for simplicity to a single cell[4], is shown on the left of Figure 1.

* Hoffman, B.F. Electrophysiology of Single Cardiac Cells, *Bull. N. Y. Acad. Med.* vol. 35, 689-709, Nov. 1959.

Actually, in making such a record of the injury potential, there is current flowing during diastole from the uninjured to the injured portion. When depolarization of this cell or group of cells occurs (labeled "systole" in the figure), all of this current of injury is dissipated and the recorder returns to zero from the less than zero level originally created by the current. The electrogram thus obtained is shown diagrammatically in the lower part of the figure on the left.

When the intracellular electrode is used, as on the right, the curve obtained is similar in form, though relatively larger for a comparable cell, since little or no current is flowing from the outside to the inside of the membrane as in the first preparation. It will be noted, too, that the connections to the galvanometer in the latter instance are the reverse of those in the former, and that the indifferent electrode is in the conducting medium surrounding the preparation.

It can readily be appreciated, upon examining the diagram on the left, how it came to be believed that excitation consisted of a wave of negativity when, in truth, what the early physiologists were observing was a reduction in the positivity of the outside of the cell during its active phase. This gave rise to the "negativity hypothesis" of electrical excitation of muscle. It is interesting that such a concept was held for many years because of an invalid interpretation of a valid experiment. The work of Craib[5] and later of Wilson, Macleod and Barker[6] gradually resulted in the universal adoption of the bipolar hypothesis[7], but not without long and at times acrimonious debate. The first recording of the intracellular potential of heart muscle[8,9] finally left no doubt about the true state of affairs in the cell during rest and during activity.

At first glance this physiological history may seem to have no great clinical implication. The truth is that it delayed for a long time the final formulation of principles for the interpretation of the precordial leads when these came into clinical use. In fact, all of us were so influenced by emphasis on negative electricity that in the initial paper on normal, unipolar precordial leads published in 1935[10], the records were made upside down compared to present custom in order to make the intrinsicoid deflection into a "chief upstroke" comparable to the intrinsic deflection of the physiological records of the day. Currently, the subject has been expanded into another controversy which revolves about whether the heart as a whole behaves as a single dipole or as multiple dipoles. This has led to an intensive study of the electric field

around the heart, and to several attempts to prove the dipolar behavior of the heart as a whole by the application of cancellation techniques to the human body[11-15].

At the clinical level, these and other similar investigations all relate to the ultimate solution of a common clinical problem. It is concerned with the answer to the question: Are the electrocardiographic abnormalities which are observed in any given record due to actual intrinsic disease of the myocardium or of the conduction system, or are they due to an unusual position of the heart in the chest? The solution ultimately relates to the establishment of a system of surface leads which will yield quite precisely the spatial electromotive force of the heart, undistorted by the effects of the conducting medium around it, or by its eccentric location within the chest.

I give you this brief review to illustrate how a relatively simple physiological technique, such as the recording of an injury potential, gave rise for a good many decades to a concept which was only gradually corrected by a great variety of observations, and was firmly settled in the end, at least so far as one aspect was concerned, by the development of the microelectrode technique of recording intracellular potentials. It is to be noted, however, that in a fashion characteristic of all biological research, the solution of one problem has given rise to a great many others.

To come to a consideration of pacemaker potentials—it is interesting that since the time of Sir Thomas Lewis, when the electrocardiographic features of a variety of arrhythmias first were described, little progress was made until recently, either in the understanding of the mechanisms involved or in the therapy used for tachycardia, fibrillation or flutter. The records of the transmembrane potential in pacemaker tissue which you have seen bode well for additional progress in this field soon. For reorientation purposes, the monophasic action potential of the sino-atrial node of the rabbit, made by my colleagues, Drs. Kleinfeld and Stein, with the help of Mr. Magin, is shown in Figure 2. As discussed earlier this evening by Dr. Hoffman*, it reveals the characteristic loss of the transmembrane potential during diastole until the firing or threshold level is reached, and only then is the impulse propagated. This diastolic loss of potential is due to the natural incapacity of pacemaker cells to maintain intact impedance during diastole. It would seem reasonable to believe that in the clinical case of tachycardia or premature systoles

* See footnote, page 4

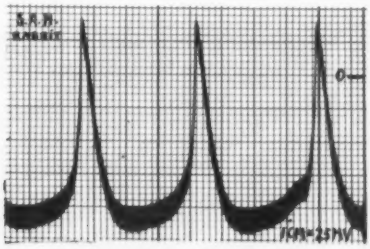

Figure 2. An intracellular potential made from the region of the sino-atrial node of a rabbit, demonstrating the diastolic loss of potential characteristic of pacemaker tissue. Calibration, 1 cm. = 25 mv. Time lines, 0.04 sec. (From Kossmann, in *Advances in Electrocardiography*[4].)

a cell or group of cells somewhere in the heart, either normally or as a result of disease, displays a similar dissipation of the transmembrane potential during diastole and ultimate propagation of an impulse. The speed of this phenomenon will determine in part whether the clinical effect will be extrasystoles, an abnormal rhythm, or a tachycardia.

With regard to circus rhythm, other factors undoubtedly are involved, such as the duration of the refractory period, and here choline plays an important part. This fact has been relearned by the recent experimentation principally of Burn, Williams and Walker[16], but was suspected for a long time as a result of the ease with which fibrillation of the atria could be produced by vagal stimulation in conjunction with other manipulations. At the moment, there is not much in this area of immediate use to the clinician. Nevertheless it would seem prudent to follow these physiological investigations quite carefully, for with increased knowledge of the prepotential, the factors concerned with alteration of the threshold potential, and the relationship of choline, 5-hydroxytryptamine, and probably other naturally occurring agents to the transmembrane potential, there will undoubtedly be advances of eventual use at the bedside.

One of the less satisfactory aspects of clinical electrocardiography is the matter of block, both intraventricular and atrioventricular. Present concepts localize this block to some part of the conduction system. From what has been observed with the microelectrode it would seem that block can be observed at the cellular level. If depolarization of the ventricular cells is slowed, widening of QRS in a surface lead will occur. If depolarization fails completely and in all ventricular cells, then complete block will ensue.

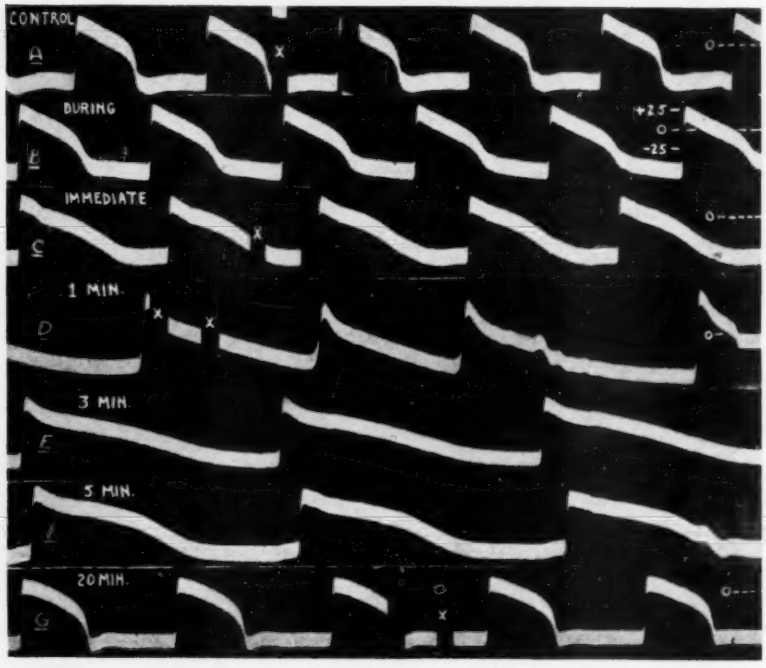

Figure 3. Sequential effects of barium chloride (5 mg./kg.) injected into the aorta on the membrane action potential of ventricular fibers of the frog heart. The prematurity, and long rise time, of depolarization and the smaller resting potential are to be noted in the middle two complexes of record D. (There is artefact on the repolarization phase of the second.) Calibration is shown in record B (0.9 cm. = 50 mv.). Time lines 0.04 sec. X indicate where a standardization voltage was introduced. (From Kleinfeld, Stein, and Meyers[17], *Circulation Res. 2*:488-93, 1954. Reproduced by permission of the authors.)

The evidence for cellular block, as it might be called, is of several types. For example, the action potential of the frog ventricle in Figure 3 illustrates the sequential effects of 5 mg. per kg. of barium chloride injected into the aorta[17]. There is a gradual lengthening of the repolarization process, particularly its third phase, but over a period of 20 minutes there is a return to the control configuration. To be noted is the record taken one minute after injection. In the middle of it are two beats, probably of ectopic origin, since both were premature relative to the remainder. Both of these show a rate of depolarization, and incidentally a magnitude of resting potential, which is somewhat less than in the action potential on either end of the strip. The slowed spike can be interpreted as a partial block of depolarization which should

manifest itself as a widened QRS interval in a surface lead.

Another piece of evidence in this direction is the demonstration of the existence of alternation of the action potential. Alternation both in magnitude and duration of any part of the membrane action potential, including the after-potential, has been observed by Kleinfeld, Stein and Magin[18] in our laboratory. In the case of pacemaker tissue under the influence of a choline esterase inhibitor, alternation of a type may occur in which every second beat fails to reach the threshold level and the intracellular equivalent of 2:1 sino-atrial block develops.

Other agents and procedures can slow the rise time of depolarization. Potassium in high serum concentration does it clinically, and, as used for inducing cardioplegia, can prevent the action potential completely.

All of these observations on different grades of impairment of depolarization suggest that there may be such a spontaneous clinical entity as intraventricular block or even complete block of depolarization at the myocardial level. Certainly many aspects of bundle-branch block and atrioventricular block are most difficult to explain in terms of the conventional point of view. It is visualized that clarification will come only with precise studies such as were presented earlier in this scientific session.

Clinical Aspects of the Interrelations Between Electrolytes and the Transmembrane Myocardial Potential

In the area of electrolytes, relative to clinical behavior of the myocardium, a good deal more can be said of a definitive nature. The most significant advances in the clinic have been made in the field of the interrelationships of potassium, calcium and digitalis. It is perhaps easiest to present them in relation to each other, because ordinarily the effects of digitalis are opposed by potassium and augmented by calcium. The latter is an old clinical observation made in 1936[19], when it was discovered that calcium given intravenously to a digitalized patient could be fatal. This observation seems to have been forgotten or sometimes overlooked during surgery, and it is suspected that on some occasions where cardiac arrest has occurred in the operating room and cardiac massage instituted along with the injection of calcium, the result was unfavorable because it was forgotten that the patient was digitalized.

Hypocalcemia induces fairly characteristic changes in the electro-

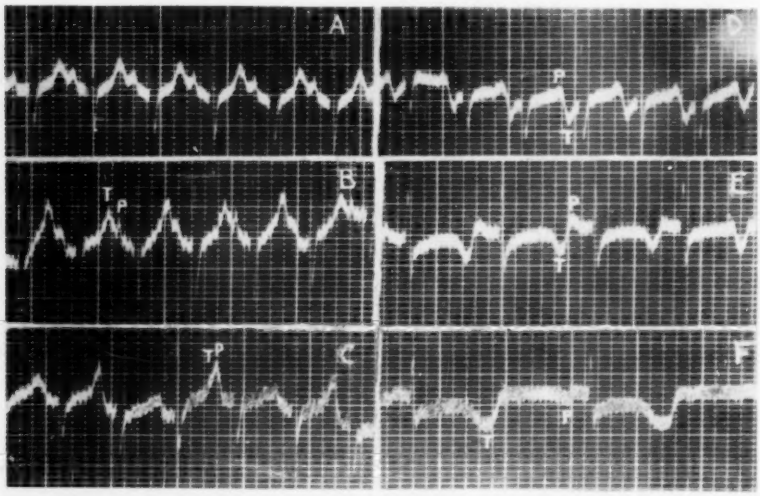

Figure 4. Effects of intravenous EDTA (50 mg./kg.) on lead II of the rabbit electrocardiogram. A, control (rate 333/min., Q-T 0.12 sec., K = 0.28); B, during administration of drug (T waves taller and peaked, Q-T 0.15 sec.; K = 0.36); C, immediately after injection (alteration of T waves, Q-T interval 0.14 sec., K = 0.34); D, 30 sec. after injection (T wave inverted); E, 60 sec. after injection (rate 214/min., Q-T 0.20 sec., K = 0.38, T wave negative); F, 130 sec. after injection (rate 111/min., P wave inverted as a result of shift of pacemaker to A-V node, S-T junction and segment depressed, T inverted, Q-T 0.27 sec., K = 0.37). (Modified from Kleinfeld and Gross[28], *Amer. J. Physiol. 187:* 479-82, 1956. Reproduced by permission of the authors and the publication.)

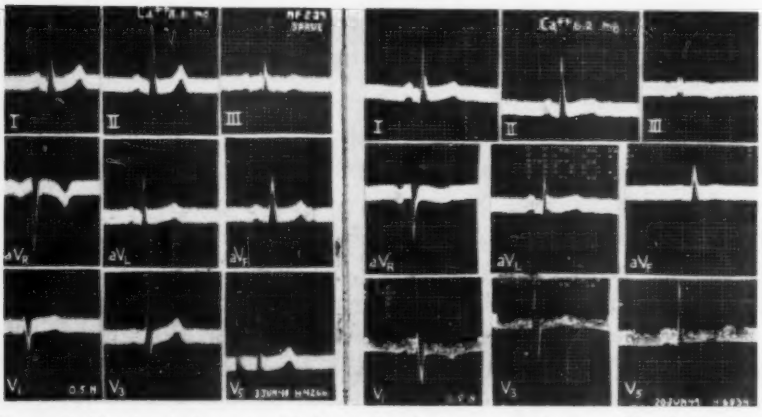

Figure 5. Non-tropical sprue with hypocalcemia in a man 39 years old, admitted for recurrent fractures. The electrocardiogram on the left was recorded when the serum Ca was 8.6 mg./100 ml.; on the right when it was 6.2 mg./100 ml. Although there are differences in the form of the final ventricular deflections between the two records, the Q-T intervals are identical (0.36 sec.) and the systolic indices almost so (0.414, 0.405). The status of the other serum electrolytes was unknown at the time of the recordings but on other occasions these were not abnormal.

cardiogram. Figure 4 illustrates what happens when 50 mg./kg. of ethylenediamine tetra-acetic acid, as the disodium salt, is injected into a rabbit[20]. This chelating agent will remove ionized calcium from the blood stream. A is the control; B is immediately after injection and shows some prolongation of the Q-T interval and a change in form of the T wave; C discloses alternation of the T wave; and D, E, and F, inversion of this deflection. The slow rate in the last record is the result of atrioventricular nodal rhythm. Inversion of the T wave may be seen in the hypocalcemia of spasmophilia in children. In adults the most frequent abnormality is a prolonged Q-T interval, but the magnitude and direction of the recovery process may be altered sufficiently to give some changes in T wave as seen in a case of non-tropical sprue (Figure 5). The hypocalcemic record is on the right, where the T wave in leads V_1 and V_3 is to be compared with the control T wave in these leads on the left. The serum calciums are indicated at the top of each electrocardiogram. Other electrolytes were not measured at the time, but were not abnormal on other occasions. Interestingly, the Q-T intervals in the two records were identical (0.36 sec.) and the systolic indices were 0.414 and 0.405, both within normal limits.

To illustrate an important point, Figure 6 shows what happens when the isolated frog heart is perfused with Ringer's solution, Ringer's solution with half calcium, and finally calcium-free Ringer's solution for different intervals of time[4]. In this preparation the direct cardiac output was simultaneously measured with the ventricular action potential. It will be noticed that the control output was 4.2 ml. per minute, that five minutes after perfusion with half-calcium Ringer's solution the action potential had not changed a great deal, nor had the rate, but that the cardiac output began to fall. Lastly, after a prolonged period of perfusion without calcium, the cardiac output became almost nothing, yet the action potential showed little change, other than some prolongation of the plateau portion of the repolarization phase. This would illustrate what is now fairly well known, namely, that calcium is essential for excitation-contraction coupling. The figure illustrates dissociation of this coupling induced by hypocalcemia.

The known additive effects of calcium and digitalis have led to the development of two clinical tests which may eventually be proven to have some value, although both are potentially hazardous. The first of these is the test described by Gubner and Kallman[21], concerned with

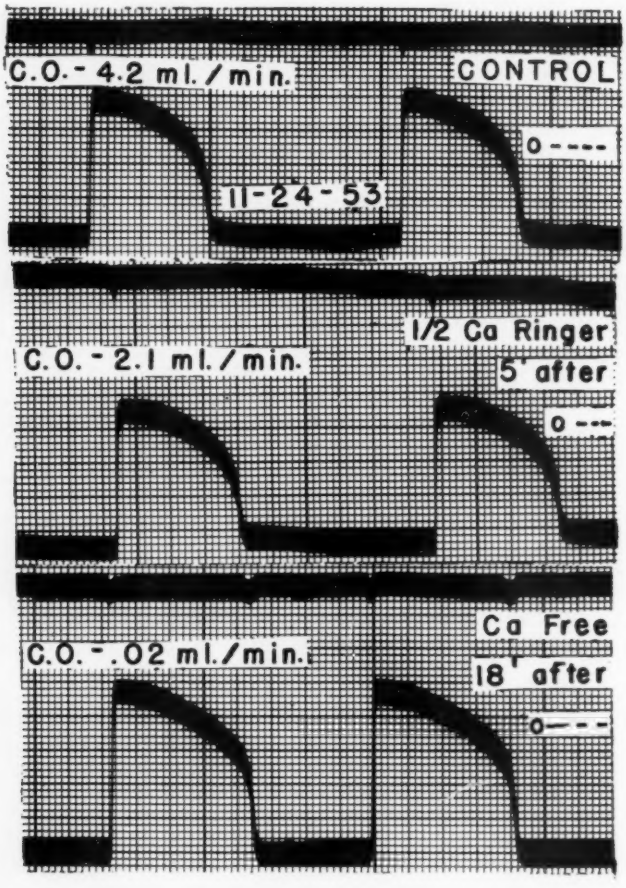

Figure 6. Effect of decreasing the calcium in the perfusing Ringer's solution on the electrical and mechanical activities of the isolated perfused frog ventricle. Simultaneous records are of the indirect bipolar electrocardiogram (above—low amplitude trace) and of the single fiber membrane action potential (below). Cardiac output (C. O.) was determined just before recording the electrical potentials. Time lines 0.04 sec. Calibration for intracellular potential, 0.9 cm. = 50 mv.; for electrocardiogram 1.0 cm. = 1.0 mv. (From Kleinfeld, Ch. 3 in Kossmann's *Advances in Electrocardiography*[4].)

the intravenous injection of the disodium salt of ethylenediamine tetra-acetic acid. The chelating agent will remove ionized calcium from the blood stream. However, to achieve this, a continuous infusion must be given, and the recommended rate is approximately 15 mg. per minute. When this is given to a patient who has the cardiac manifestations of digitalis toxicity, these manifestations during the course of the infusion

may disappear. The clinical application of the test would be to demonstrate that an arrhythmia or some other abnormality in the record is in truth due to digitalis rather than intrinsic disease, and at the same time to terminate a potentially dangerous toxic rhythm if this should be present.

Another clinical procedure, the calcium-digitalis tolerance test, has been described in some detail by Nalbandian, Gordon and Kaufman[22]. This test is an endeavor to quantitate the degree of digitalization of a patient. It is the reverse procedure of the EDTA test, calcium being given intravenously as a 10 per cent solution of $CaCl_2$ in progressively larger increments. This is done over a period of 20 minutes or until such time as distinct evidence of digitalis toxicity appears. The authors have worked out some calculations whereby the percentage of total digitalization in any particular patient can be estimated. The quantitative aspects of the method are indeed attractive but the known hazards of the simultaneous use of calcium and digitalis make it prudent to do additional observations under controlled conditions before the test is accepted for general clinical usage.

Potassium has received more attention at the clinical level than any other electrolyte. The use of it in concentrated form by the surgeon to induce cardioplegia during open heart surgery has already been mentioned. It is most often utilized by the medical man in the treatment of digitalis toxicity, and almost every clinician is aware of the usefulness of this drug in eliminating or decreasing the toxic effects of digitalis, especially in the patient with advanced heart disease. The frequent occurrence of atrial tachycardia with 2:1 A-V block as a manifestation of digitalis toxicity, which may be relieved by potassium even though the serum potassium may be normal, is something which has been called to our attention by Lown and Levine[23].

The distinctive effects of potassium on the intracellular potential are mirrored quite comparably in the clinical electrocardiogram. A few examples should suffice, since these effects are fairly well known. First, with reduction in the potassium content of the serum and probably of the myocardium, there tends to be a reciprocal change in the U wave and in the T wave. As the potassium falls, the T wave goes down, often to inversion. Downward displacement of the S-T segment may also occur. Conversely, the U wave becomes more prominent. It was Surawicz and Lepeschkin[24] who called attention to the clinical fact that the

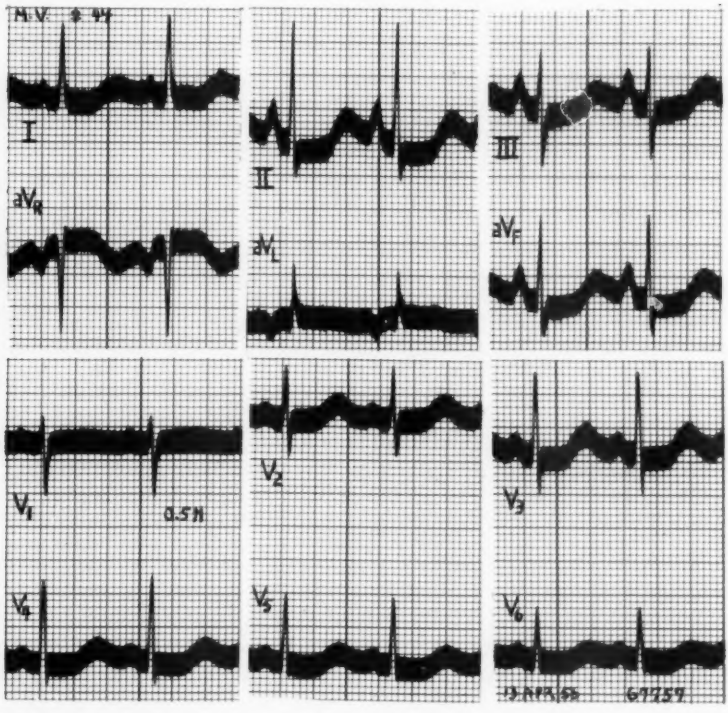

Figure 7. Electrocardiogram of a 44 year old white female (M. V.) with duodenal obstruction and vomiting for 3 weeks. The electrolyte pattern was of hypokalemic alkalosis (Table I). (From Kossmann[25], *Trans. Life Insce. med. Dir. Amer.* This Figure and Figure 8 reproduced by permission of the publisher.)

TABLE I. Table showing the time of recording the electrocardiograms of patient M. V. reproduced in Figs. 7 and 8 in relation to the serum electrolytes and BUN before (13 Apr. '56) and after the institution of corrective therapy. (From Kossmann[25]. Reproduced by permission of the publisher.)

Pt. M. V. ♀ *44*	*13 Apr. 56*	*15 Apr. 56*	*17 Apr. 56*	*18 Apr. 56*
EKG	Abnormal	.....	Normal	.....
BUN	37.1*	21.4	.....	23.7
Na	138.0	135.0	.....	135.0
K	2.0	2.8	.....	4.8
Cl	.....	86.9	.....	97.6
HCO_3	52.2	34.0	.....	27.3
Ca	11.1	.....	.....	.....
P	3.8	.....	.....	.....

* BUN, Ca and P in mg./100 ml.; others in mEq./L.

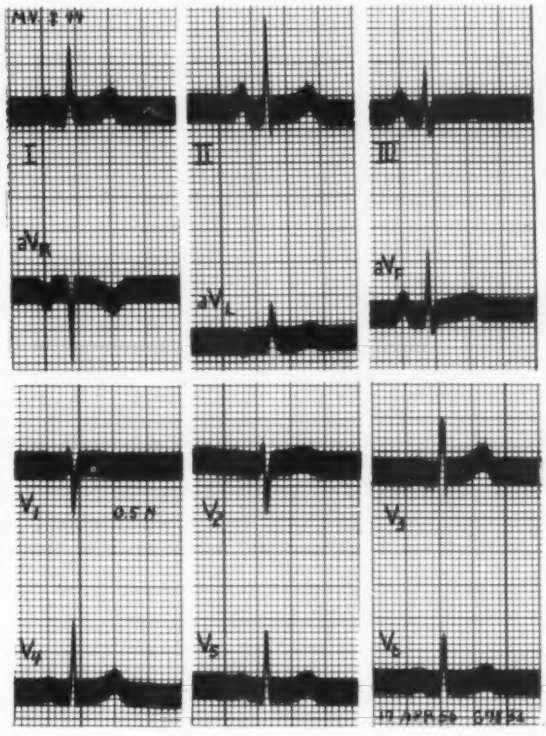

Figure 8. Normal electrocardiogram of patient M. V. recorded four days after the one shown in Fig. 7, and after the correction of hypokalemia, alkalosis, and azotemia. (From Kossmann[25].)

duration of the Q-T interval was actually not prolonged in potassium deficiency, but rather that it appeared to be prolonged simply because the U wave, related to the after-potential of intracellular records, was exaggerated.

It is not ordinarily appreciated how striking these changes may be in the clinical electrocardiogram, and to illustrate this I show the following (Figure 7) record of a young woman who was vomiting for a period of three weeks as a result of pyloric obstruction[25]. As you can see, the changes, especially in the S-T segment, T wave, and not easily discerned U wave, are most pronounced, and if the record were seen by itself, it might not be suspected of being on the basis of simple electrolytic disturbance. The biochemical and electrolytic data, which indicate the existence of a hypokalemic alkalosis at the time of the first

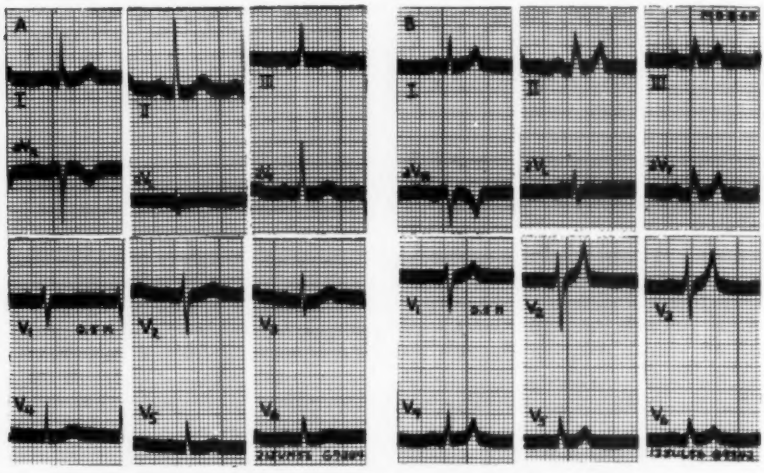

Figure 9. Electrocardiograms of a 60 year old white female before (A, 21 Jun. '56) and after (B, 13 Jul. '56) subtotal gastrectomy with duodenal drainage performed on 25 Jun. '56. Because of bleeding, she received 13 units before and just after operation. Between 9 Jul. '56 and 12 Jul. '56 she received 1 liter of 5 per cent dextrose in distilled water daily, with 40 mEq. of potassium added to the last bottle. The abnormal record, B, shows the characteristic lowering of the voltage of QRS, widening of the QRS interval, shortening of the Q-T interval, and sharply pointed high T wave when the serum K was 6.8 mEq./L. (see Table II).

TABLE II. Biochemical data obtained on patient M.D., a 60 year old woman whose electrocardiograms are shown in Figure 9. To be noted are the abnormalities on July 13, which was the day of the abnormal electrocardiogram of Figure 9B. The principal abnormalities were azotemia, hyponatremia, hyperkalemia, hypochloremia and acidosis.

Pt. M.D. ♀ *60*	IATROGENIC HYPERKALEMIA				
	21 Jun.	*26 Jun.*	*3 Jul.*	*6 Jul.*	*13 Jul.*
EKG	Normal	.....	.....	.....	Abnormal
BUN	11.7*	.....	30.6	19.0	71.2
Na	.....	139.0	131.0	131.0	118.0
K	.....	3.3	4.7	4.3	6.8
Cl	.....	104.3	104.2	103.8	87.1
HCO_3	.....	27.3	24.0	23.1	19.7

* Units as in Table I.

electrocardiogram, and its gradual correction by therapy, are shown in Table I. The electrocardiogram taken four days after the first (Figure 8) is completely normal at a time when there has been re-establishment of normal serum potassium and dissipation of the alkalosis.

In contrast, the effects of high potassium, also well known, are

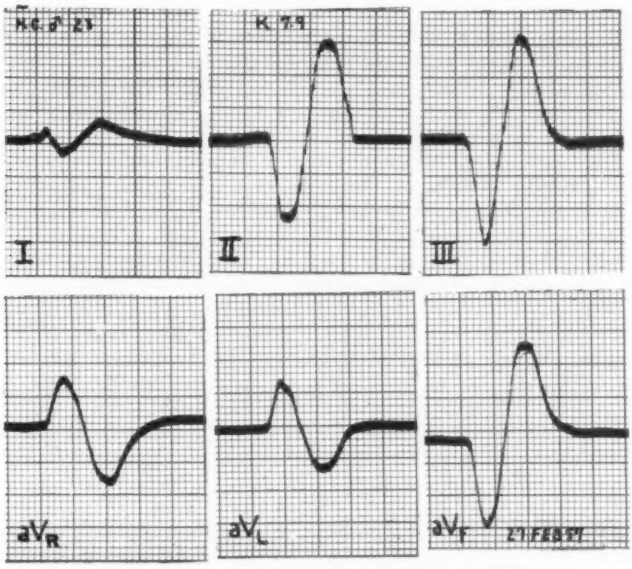

Figure 10. Terminal electrocardiogram of a 23 year old male heroin addict who, while in jail, attempted suicide by hanging four days before. A lower nephron nephrosis developed and on the day of the electrocardiogram and death the following blood chemistries were obtained: K 7.9 mEq./L.; BUN 180 mg./100 ml.; pH 7.27; CO_2 8.71 mEq./L. To be noted are the bizarre, wide QRS complexes fusing imperceptibly into the final ventricular deflections, the opposite directions of the initial and final ventricular deflections, and the absence of evidence of atrial activity. The rate of the idioventricular pacemaker was less than 50 beats per minute and irregular.

illustrated in Figure 9 and Table II. The earliest change seen is a shortening of the Q-T interval and a greater sharpness of the T waves (Figure 9B). This fits in with the shortening of the repolarization process of the intracellular record when the extracellular potassium is increased. In more advanced stages of the situation there is an increase in the duration of intraventricular conduction and continued shortening of the recovery period, so that one gets the easily recognizable picture of a long QRS interval with a short Q-T interval (Figure 9B). An illustration of these effects is well shown in Figure 9 since a control record was available (Figure 9A). This 60 year old white woman had a subtotal gastrectomy with duodenal drainage. In addition to early postoperative transfusions she was given intravenous fluids from 9 July to 12 July consisting of 5 per cent dextrose in distilled water, with added potassium on one occasion but no sodium. The results of this therapy on the serum electrolytes are shown in Table II, and the elec-

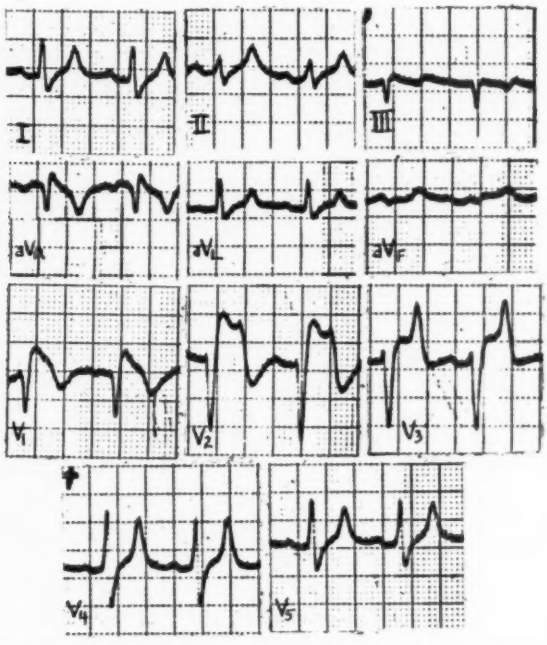

Figure 11. Postcholecystectomy transfusion reaction with lower nephron nephrosis and hyperkalemia in a 43 year old male. A few days before the above electrocardiogram was made, the BUN was 146 mg./100 ml. and the K 6.6 mEq./L., but the electrocardiogram was still normal. After dialysis on the artificial kidney the above abnormalities, consisting of a wide QRS interval, a short Q-T interval, and unusual elevation of the S-T segments in leads V_1 to V_3 disappeared. The patient went on to die, but showed no evidence of myocardial disease at necropsy. (Reproduced by courtesy of Dr. Calvin Kay of Philadelphia.)

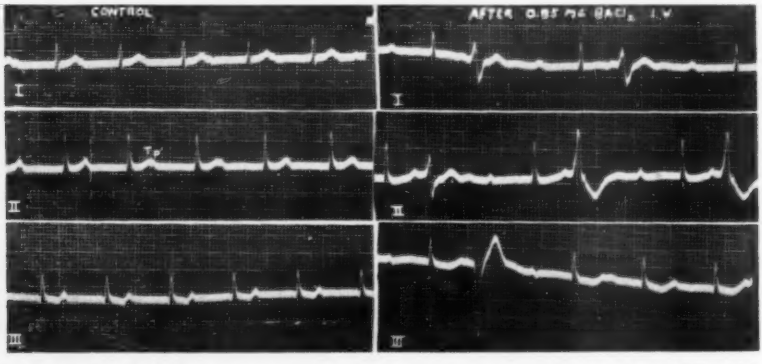

Figure 12. Effect of intravenous Ba Cl_2 (0.85 mg.) in a male patient in his middle fifties with no evidence of heart disease other than a prolonged P-R interval (0.44 sec.). The drug had no effect on the latter except to prolong it slightly (0.46 sec.), but did cause evanescent ventricular premature systoles with coupling.

trocardiographic alterations caused by the iatrogenic hyperkalemic acidosis are shown in Figure 9B. In the agonal stages the QRS and T may be quite bizarre and atrial activity not apparent (Figure 10). An interesting record is the next one, which was lent to me by Dr. Calvin Kay of Philadelphia (Figure 11). It was taken on a man who, after a cholecystectomy, went into shock and developed a lower nephron nephrosis. The record that you see was taken at a time when the BUN and the serum potassium were abnormally high. It shows unusual elevation of the S-T segment in leads V_1 to V_3, an abnormality which is occasionally seen in hyperkalemia. This patient, at the time, was suspected of having some intrinsic cardiac disease as well as azotemia. He was placed on the artificial kidney with a temporary restitution of a normal electrolyte balance; the electrocardiogram then became entirely normal. Levine, Wanzer and Merrill[26] observed this reversal of the S-T displacement of hyperkalemia some time ago and have spoken of it as the "dialyzable current of injury". Parenthetically, despite the therapy, this patient died, and at necropsy showed no evidence of organic disease of the coronary arteries or of the myocardium.

There are other electrolytes which may prove to have greater clinical importance than they do at present, by virtue of the studies being made of them and their effects on the transmembrane potential. I have already shown one experimental effect of barium (Figure 3). Older clinicians will remember that in the early 1930's barium was suggested as a drug to be used in complete heart block. I show you one record (Figure 12) of a man who had only incomplete A-V block, but we made a great many observations on him with varying oral and intravenous doses of barium. All that the drug did was to produce extrasystoles, which theoretically may be of use with a faulty idioventricular pacemaker, but had little effect, in this one patient, on atrioventricular conduction.

The popularity of molar sodium lactate for the treatment of complete heart block, as far as I know, has not been studied at the membrane level, but it would seem that the change in pH of the perfusion milieu produced by this agent must have effects on the impedance of the myocardial membrane and the gradient of ions that exists across it.

We have some observations also on the effects of cadmium and of lithium[27, 28], and others have data on magnesium and strontium[29-31], but since these, with the exception of magnesium, have no immediate clinical application, I shall not discuss them at this time.

Summary

There can be no question that the newer physiology of the myocardium as revealed here today will be a most important part of the Medicine that we practice tomorrow. I hope I have demonstrated, too, that the Medicine of yesterday has at least pointed the way in many instances to approaches and paths of investigation which today are yielding such fruitful results by the superb techniques available for measuring intracellular potentials and the gradients, fluxes, and exchanges of electrolytes across the myocardial membrane. Although those of us primarily concerned with the health of the whole man can only have feelings of inferiority in the presence of those who have mastered such quantitative physiological methods, we can take solace in the knowledge that good research is good whether done on the whole man or on the membrane of one of his cells. By means of continued, painstaking clinical observation, in terms of the physiological data and methods available, the Medicine of today, as in the past, can contribute weightily to the Physiology of tomorrow.

REFERENCES

1. Matteucci, C. Note sur les phénomènes électriques des animaux, *C. R. Acad. Sci. 13*:540-41, 1841.
2. Kossmann, C. E. The electrocardiographic effects of myocardial and pericardial injury, *Bull. N. Y. Acad. Med. 28*:61-89, 1952.
3. Wilson, F. N., Hill, I. G. W. and Johnston, F. D. The interpretation of the galvanometric curves obtained when one electrode is distant from the heart and the other near or in contact with the ventricular surface: Part I. Observations on the cold-blooded heart, *Amer. Heart J. 10*:163-75, 1935. Part II. (Wilson, F. N., Johnston, F. D. and Hill, I. G. W.). Observations on the mammalian heart, *Amer. Heart J. 10*:176-89, 1935.
4. Kossmann, C. E. *Advances in electrocardiography*. New York, Grune & Stratton, 1958.
5. Craib, W. A study of the electrical field surrounding active heart muscle, *Heart 14*:71-109, 1927.
6. Wilson, F. N., Macleod, A. G. and Barker, P. S. *The distribution of the currents of action and of injury displayed by heart muscle and other excitable tissues*. Ann Arbor, U. of Michigan Press, 1933.
7. Macleod, A. G. The electrogram of cardiac muscle: I. An analysis which explains the regression or T deflection, *Amer. Heart J. 15*:165-86, 1938. II. The lengths of the stages of activity, *Amer. Heart J. 15*:402-13, 1938.
8. Coraboeuf, E. and Weidmann, S. Potentiels d'action du muscle cardiaque obtenus à l'aide de microélectrodes intracellulaires. Présence d'une inversion de potentiel, *C. R. Soc. Biol. 143*:1360-61, 1949.
9. Woodbury, L. A., Woodbury, J. W. and Hecht, H. H. Membrane resting and action potentials of single cardiac muscle fibers, *Circulation 1*:264-66, 1950.
10. Kossmann, C. E. and Johnston, F. D.

The precordial electrocardiogram. I. The potential variations of the precordium and of the extremities in normal subjects, *Amer. Heart J. 10*:925-41, 1935.

11. Schmitt, O. H., Levine, R. B. and Simonson, E. Electrocardiographic mirror pattern studies: I. Experimental validity tests of the dipole hypothesis and of the central terminal theory, *Amer. Heart J. 45*:416-28, 1953. II. (Levine, R. B., Schmitt, O. H. and Simonson, E.). The statistical and individual validity of the heart dipole concept as applied in electrocardiographic analysis, *Amer. Heart J. 45*:500-18, 1953. III. (Simonson, E., Schmitt, O. H., Levine, R. B. and Dahl, J.). Mirror pattern cancellation in normal and abnormal subjects, *Amer. Heart J. 45*:655-64, 1953.
12. Frank, E. Measurement and significance of cancellation potentials on the human subject, *Circulation 11*:937-51, 1955.
13. McFee, R. and Johnston, F. D. Electrocardiographic leads: I. Introduction, *Circulation 8*:554-68, 1953. II. Analysis, *Circulation 9*:255-66, 1954. III. Synthesis, *Circulation 9*:868-80, 1954.
14. Brody, D. A. and Copeland, G. D. Electrocardiographic cancellation: some observations concerning the "nondipolar" fraction of precordial electrocardiograms, *Amer. Heart J. 56*:381-95, 1958.
15. Burger, H. C. Lead vector projections. I. *Ann. N. Y. Acad. Sci. 65*:1076-87, 1957.
16. Burn, J. H., Vaughan Williams, E. M. and Walker, J. M. The production of block and auricular fibrillation in the heart-lung preparation by inhibitors of cholinesterase, *Brit. Heart J. 17*:431-47, 1955.
17. Kleinfeld, M., Stein, E. and Meyers, S. Effects of barium chloride on resting and action potentials of ventricular fibers of the frog, *Circulation Res. 2*: 488-93, 1954.
18. Kleinfeld, M., Stein, E. and Magin, J. Electrical alternans in single ventricular fibers of the frog heart, *Amer. J. Physiol. 187*:139-42, 1956.
19. Bower, J. O. and Mengle, H. A. K. The additive effect of calcium and digitalis, *J. Amer. med. Assoc. 106*:1151-53, 1936.
20. Kleinfeld, M. and Gross, M. Electrocardiographic manifestations of hypocalcemia produced with ethylenediamine tetraacetic acid, *Amer. J. Physiol. 187*: 479-82, 1956.
21. Gubner, R. S. and Kallman, H. Treatment of digitalis toxicity by chelation of serum calcium, *Amer. J. med. Sci. 234*:136-44, 1957.
22. Nalbandian, R. M., Gordon, S. and Kaufman, J. Calcium—digitalis tolerance test. A clinical report of the first 24 trials, *Amer. J. med. Sci. 234*:391-402, 1957.
23. Lown, B. and Levine, H. D. *Atrial arrhythmias, digitalis, and potassium.* New York, Landsberger Medical Books Inc., 1958.
24. Surawicz, B. and Lepeschkin, E. The electrocardiographic pattern of hypopotassemia with and without hypocalcemia, *Circulation 8*:801-28, 1953.
25. Kossmann, C. E. The effect of myocardial disease and dysfunction on the form of the electrocardiogram, *Trans. Life Insce. med. Dir. Amer. 41*:101-31, 1957.
26. Levine, H. D., Wanzer, S. H. and Merrill, J. P. Dialyzable currents of injury in potassium intoxication resembling acute myocardial infarction or pericarditis, *Circulation 13*:29-36, 1956.
27. Kleinfeld, M., Greene, H., Stein, E. and Magin, J. Effect of cadmium ion on the electrical and mechanical activity of the frog heart, *Amer. J. Physiol. 181*:35-38, 1955.
28. Stein, E., Kleinfeld, M., Greene, H. and Meyers, S. Action of lithium chloride on the isolated perfused frog heart, *Amer. J. Physiol. 183*:121-24, 1955.
29. Szekely, P. and Wynne, N. A. The effects of magnesium on cardiac arrhythmias caused by digitalis, *Clin. Sci. 10*:241-53, 1951.
30. Hoffman, B. F. and Suckling, E. E. Effect of several cations on transmembrane potentials of cardiac muscle, *Amer. J. Physiol. 186*:317-24, 1956.
31. Garb, S. The effects of potassium, ammonium, calcium, strontium, and magnesium on the electrogram and myogram of mammalian heart muscle, *J. Pharmacol. 101*:317-26, 1951.

INFLUENZA AND UPPER RESPIRATORY INFECTIONS

*Transcription of a Panel Meeting**

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MODERATOR WALSH MC DERMOTT: The subject of this afternoon's panel meeting is *Influenza and Upper Respiratory Infections.* I shall first call on Dr. Rose and ask him to define the title *Infections of the Upper Respiratory Tract.*

DR. HARRY M. ROSE: I think we must consider it in two ways. We have to regard this in connection with various types of etiologic agents which may be responsible for infection and then with the different types of involvement of the respiratory tract which they may cause.

So far as viral agents are concerned, a variety of syndromes may occur in upper respiratory infections, varying from those which resemble the so-called common cold or coryza, down to and including rather extensive involvement of the lung, in what might be called viral pneumonia, for want of a better term.

Fortunately we have arrived at a period in development when, in many instances, it is possible to tell precisely what the etiologic factors are. Roughly, this also applies with respect to a variety of bacterial agents.

MODERATOR MC DERMOTT: *Do you think they can be divided into pneumonias, bronchitis and infections in areas of the upper respiratory tract, or are they all one process?*

DR. ROSE: I think the clinician ordinarily tends to assign some descriptive term or phrase to the infection, depending upon which clinical manifestations are dominant, and also the extent to which the respiratory tract becomes involved, whether this be in the upper respiratory tract itself or whether the lung is involved also.

MODERATOR MC DERMOTT: *Dr. Rogers, would you agree with that general description?*

DR. DAVID E. ROGERS: I think I would. There are some microbial parasites that quite characteristically produce disease of the lung parenchyma. These could not be considered upper respiratory tract infections but this might be an appropriate area for this panel to consider. I would divide these infections this way in my therapeutic thinking.

MODERATOR MC DERMOTT: *Whether pneumonia is present or is not present?*

DR. ROGERS: Yes.

MODERATOR MC DERMOTT: *How many bacteria cause primary disease of the upper respiratory tract? How many bacteria do you have to work on?*

DR. ROGERS: It depends upon the age group. Certainly in the adults there are very few.

MODERATOR MC DERMOTT: *Except streptococcal pharyngitis?*

DR. ROGERS: With the exception of the streptococcal pharyngitis, I am inclined to think other bacteria very rarely cause any primary disease in the upper respiratory tract.

MODERATOR MC DERMOTT: *So when we are speaking of primary disease, the upper respiratory infections, except streptococcal infections, are essentially all viral infections?*

DR. ROGERS: Yes.

MODERATOR MC DERMOTT: *This is not the case with pneumonias?*

DR. ROGERS: No.

MODERATOR MC DERMOTT: *Do you agree with that, Dr. Kilbourne?*

DR. EDWIN D. KILBOURNE: I do. There is a big advantage in making regional differentiation and localization of infections. One can make fairly sharp inferences from this type of localization. If one is dealing primarily with a pharyngeal involvement, I think he has advanced the situation etiologically in making this distinction and one might then infer that if there is bacterial disease present it probably is due to group A streptococcus or, if the disease has more the characteristics of viral infection, that it may be related to adenovirus infection. This point may be a little thin, a little fine. I know some are unwilling to make precise distinctions between various degrees of pharyngeal infection as opposed to concomitant lymphadenopathy. I feel it is very useful if one has experience in this area.

MODERATOR MC DERMOTT: *Let us take a concrete case. A 17 year old boy awakes in the morning and complains of sore throat, he does not vomit, he has a temperature of 102.5° F. and on examination has an inflamed pharynx, some patches of exudate and some tender lymph nodes in the neck and the white count shows 9,000 cells, what are the possibilities there? What would your management be?*

DR. KILBOURNE: I would say the possibilities are not as unlimited as might appear at first blush. One has to be arbitrary in these cases when dealing at the clinical level. The obvious chief possibilities would be, in this case, a streptococcal pharyngitis as a possible bacterial cause and of the viruses, members of the adenovirus group, if actual pharyngeal soreness was complained of, with lymphadenopathy.

MODERATOR MC DERMOTT: *The adenoviruses, then, can cause a sore*

throat, an illness that can resemble a streptococcal sore throat?

DR. KILBOURNE: They can indeed, as Dr. Rose probably knows better than I. And those who were involved in the Respiratory Disease Commission in World War II found difficulty, in at least one outbreak, in differentiating what later proved to be (in retrospect) adenovirus infection from group A hemolytic streptococcal infection, to the extent that one could even find descriptions of exudate, pharyngeal exudate, in the presence of what, again retrospectively, we know were adenovirus infections. Any case such as you describe would have to be treated as a group A streptococcal infection, were there any doubts.

MODERATOR MC DERMOTT: *What are the percentage chances of its being one? In other words, how far off are you in treating the one out of four? Do you agree, Dr. Rose, that the pharyngitis as described could be caused either by adenovirus or streptococcal illness?*

DR. ROSE: I certainly do. One of the points that you made in connection with your brief history made the diagnosis to my mind a little more difficult. You mentioned that this hypothetical patient had a white count of 9,000. I am sure you did that deliberately.

MODERATOR MC DERMOTT: That is correct.

DR. ROSE: If you had told the panel that the boy had a white count of 15,000, then I think the chances would probably be 20 to 1 that he had a streptococcal infection.

MODERATOR MC DERMOTT: *Would you agree with that?*

DR. KILBOURNE: I am embarrassed about percentages, but I would go along with that.

MODERATOR MC DERMOTT: All biology is inexact, Dr. Kilbourne!

DR. KILBOURNE: I would like to point out, too, that Dr. McDermott also deliberately mentioned something which would be somewhat against the strep diagnosis. That was the absence of vomiting. Although vomiting is a little more common in people younger than 17, it is an important point in reflecting the greater toxicity of streptococcal infections.

MODERATOR MC DERMOTT: I am afraid I interrupted Dr. Rose who was making a point that the total white count of 9,000 made him shy away from the diagnosis of streptococcal disease, or rather that if the leukocyte count were 15- or 18,000, there would be a 20 to 1 chance of a streptococcal infection.

DR. ROSE: It did not make me shy away from the diagnosis, Dr. Mc-

Dermott. However, in a situation of this sort, if there is a relatively marked elevation of the white count, particularly if polymorphonucleosis is associated with it, as generally it is, the diagnostic chances are greatly increased that one is dealing with streptococcal pharyngitis. This does not, of course, invariably exclude the possibility of an adenovirus infection or, indeed, something else, because as you also intimated, biological science is by no means exact. Biological manifestations vary over wide limits.

There is one thing I might say in connection with this same hypothetical patient. You stated that he was a 17 year old boy but you said nothing about his geographical surroundings. You said nothing about his environment. If this 17 year old boy –

MODERATOR MC DERMOTT: Let us put him in Utica, New York!

DR. ROSE: If the 17 year old boy is in Utica, New York, and is attending high school, I think that his chances of having adenovirus infection are considerably less than if he happened to be the same age, or better still, a couple of years older, and were a military recruit.

MODERATOR MC DERMOTT: *If he were a 17 year old enlistee in the Marines?*

DR. ROSE: Were he a 17 year old enlistee in the Marines in basic training, then I think his chances of having adenovirus infection would be much improved.

DR. KILBOURNE: About 20 to 1.

MODERATOR MC DERMOTT: *You could take 20 to 1 there. Now we are beginning to get some clarification. If the boy were in Utica, New York, first, Dr. Rogers, do you concur with the opinions Dr. Kilbourne and Dr. Rose expressed?*

DR. ROGERS: Yes, though there are some other diagnostic possibilities that might be mentioned. This boy might have infectious mononucleosis; or this might be the prodrome of one of the exanthemata. He might have measles.

MODERATOR MC DERMOTT: *Dr. Kilbourne said that it was impossible to tell precisely whether this was a bacterial or nonbacterial infection, but in these particular circumstances, for practical purposes he would favor going ahead and treating the boy as if he had a streptococcal pharyngitis. Would you agree with that?*

DR. ROGERS: I would.

MODERATOR MC DERMOTT: *You, Dr. Rose?*

DR. ROSE: I would, indeed.

MODERATOR MC DERMOTT: *So all the panel would concur as to treatment of the boy. How long would you treat him, Dr. Rogers?*

DR. ROGERS: There is now impressive evidence to indicate that we can prevent really troublesome complications of streptococcal disease.

MODERATOR MC DERMOTT: *Such as rheumatic fever?*

DR. ROGERS: Yes, particularly rheumatic fever. This requires a program which maintains adequate penicillin levels for ten days. I would feel obligated to treat in this manner all patients who I think have streptococcal disease. This can be done in multiple ways—by giving a single shot, 1.2 million units, of benzathine penicillin, procaine, 600,000 units every other day, or with oral drug if you are willing to give it around the clock.

MODERATOR MC DERMOTT: *If the boy feels well, is afebrile two or three days later, may he go back to school?*

DR. ROGERS: He may.

MODERATOR MC DERMOTT: *May he play basketball?*

DR. ROGERS: I would be inclined to let him, but there might be some disagreement on this.

MODERATOR MC DERMOTT: *Dr. Rogers, if this be streptococcal disease, it would be important to treat for a ten day period. Dr. Kilbourne and Dr. Rose made the point that it may not be streptococcal. The circumstances would be 20 to 1 one way or the other. Would you use penicillin for a ten day period in treating people who had no streptococcal disease?*

DR. ROGERS: I might expand my answer. It is my practice to take a culture, start treatment and then combine the results of cultures with the clinical response to decide whether to continue treatment.

MODERATOR MC DERMOTT: *If the next day the culture does not show beta hemolytic streptococcus, group A, what would you do? If the patient seemed better, or somewhat better, what would you do with respect to the penicillin therapy?*

DR. ROGERS: If the boy had greatly improved by the next day and showed no beta hemolytic streptococcus in his culture, I might be inclined to continue treatment believing that I had missed the streptococci in my culture.

Commonly, patients appear a little better, though not a great deal better, the next day and do not have streptococci in the culture. I am

then quite convinced that this was not streptococcal disease and stop the treatment.

MODERATOR MC DERMOTT: *You stop the treatment. So what you try to do then is to proceed on the assumption that the patient has streptococcal disease and institute penicillin prophylaxis to circumvent rheumatic fever and other complications which may arise. In a day or so if you are more secure in your diagnosis and still want to discontinue the penicillin therapy you could do so. If, on the other hand, in a day or so you are still in an undecided state, you would continue the penicillin. If the patient were well symptomatically two or three days after this, would you make no effort to restrict his activity, or keep him in the hospital, or send him to a hospital, or keep him home?*

DR. KILBOURNE: I would like to dissent and quibble a little about this point. I would feel that if the patient were strikingly better in a day or so I would doubt the diagnosis of streptococcal pharyngitis. In that time certainly, one can have a temperature response but I think in terms of pharyngeal stiffness, soreness, lymphadenopathy, one would not expect a reversal so rapidly, even with optimal penicillin therapy. If, on the other hand, all symptoms disappear precipitately, I think it must have been something else.

MODERATOR MC DERMOTT: *You are making the point that even on the penicillin therapy a true streptococcal pharyngitis with lymphadenitis does not disappear overnight?*

DR. KILBOURNE: It does not respond like pneumococcal pneumonia.

MODERATOR MC DERMOTT: *Would you agree with that?*

DR. ROSE: I would.

MODERATOR MC DERMOTT: *How about the same problem with a six year old child with the same symptoms and, if available, the same white count?*

DR. KILBOURNE: Everyone is probably aware that the clinical spectrum of streptococcal disease in younger patients is quite different, quite varied and quite subtle, as Boisvert and others have shown some time ago. I think that in that particular situation if one has to depend upon probability or cover probabilities, I would lean more strongly to the possibility of the streptococcal diagnosis, even more strongly than in the case of the 17 year old. Although in the younger patient the fever may be absent in streptococcal infections, particularly in the very young, at the age of six one would expect some systematic reaction,

possibly no more than this.

MODERATOR MC DERMOTT: But if you treat every six year old child with a sore throat with penicillin, you are going to be treating the whole first grade the whole year.

DR. KILBOURNE: True, if sore throat is the single criterion. You mentioned fever over 102° in this particular situation and the height of the febrile response is useful as a guide in estimating the severity of the illness.

MODERATOR MC DERMOTT: *Dr. Rose, in the absence of an epidemic, how often do you see the clinical syndrome of influenza?*

DR. ROSE: I should say, Dr. McDermott, that it is by no means infrequent. I don't believe there is anything that one can call a characteristic clinical syndrome of influenza in the absence of an epidemic. If one is concerned with the sort of situation in which there is a sudden onset, a good deal of systemic reaction, moderate to marked aching of muscles, localizing signs, particularly cough, fever and some headache, this would be quite characteristic of influenza as it is seen during epidemic periods in the mildly or moderately ill patient, but it is also characteristic of infection caused by a number of other viral agents.

MODERATOR MC DERMOTT: *Would you say that there are other upper respiratory infections, exclusive of pneumonia and sore throat, in which you would favor the administration of antimicrobial drugs?*

DR. ROSE: It is difficult to answer that question. I should say, generally speaking, not unless there is some evidence of pulmonary involvement. I presume we are excluding that from the discussion at the moment?

MODERATOR MC DERMOTT: Yes. If you can convince yourself there is no such evidence.

DR. ROSE: I also assume that we are talking mainly about adult patients.

MODERATOR MC DERMOTT: Adult patients.

DR. ROSE: Not about children. As soon as we consider the younger age groups there are other etiologic agents to think about and we also encounter some of the clinical difficulties with respect to aberrant syndromes referred to by Dr. Kilbourne.

MODERATOR MC DERMOTT: *So, if you are talking about adults or 12 to 13 year old children would you say they react like adults?*

DR. ROSE: I should say so.

MODERATOR MC DERMOTT: *Twelve, 13 years, on up. Except in the instance of the pharyngitis just cited, as long as there is no evidence of pneumonia you would not want to give an antimicrobial drug in the presence of running nose, coughing, all the syndromes of respiratory infection?*

DR. ROSE: I should say not.

MODERATOR MC DERMOTT: *Would you agree, Dr. Rogers?*

DR. ROGERS: I would agree.

MODERATOR MC DERMOTT: That clarifies the situation up to this point, namely, that in a 12-13 year old or an adult, in the absence of either pharyngitis or pneumonia you see no reason for giving antimicrobial drugs.

Dr. Rose, you mentioned that the situation in children, however, might be different. Could you expand on that?

DR. ROSE: In the first place, there are probably several other viral agents one would have to consider. Although the evidence at hand is not very great at the moment, and a great deal more work remains to be done in order to elucidate the relationship of certain viral agents to syndromes such as the one under discussion, there seems little doubt that in addition to the group of adenoviruses, we should think of such agents as the hemadsorption viruses, which have been shown to produce this sort of clinical picture in children. The croup-associated agent, originally isolated by Chanock, has been found to produce this clinical pattern.

MODERATOR MC DERMOTT: *Here there are at least three respiratory infections in children that would not be helped by antimicrobial drugs but which might mimic diseases which could be helped, is that correct?*

DR. ROSE: That is correct. On the other hand, there is another bacterial agent that should be borne in mind. The six year old child, mentioned before, is getting a little bit elderly but one would certainly have to think of the possibility of Hemophilus influenzae infection. I think that the clinical pattern, as you describe it, would put the disease rather early in the course, were this to be one of the typical types of pharyngitis that one sees, and I should be very much astonished if the white count were as low as the one mentioned.

MODERATOR MC DERMOTT: *How about staphylococcal tracheobronchitis in young children?*

DR. ROSE: It is a possibility.

MODERATOR MC DERMOTT: *So we have certain bacterial infections*

at the early ages of three or four years, that do not have to be considered when handling the adult patient. Dr. Rogers, would you agree with that?

DR. ROGERS: I would certainly feel that both of these bacterial parasites cause disease in the very young, principally below the age of two.

MODERATOR MC DERMOTT: Below the age of two. I misspoke.

Dr. Rose has told us that the influenza syndrome one sees in an epidemic may also be seen in the absence of epidemics. In addition, it is extremely difficult to identify this syndrome in that so many gray areas occur on the edges. I think that was your position, Dr. Rose?

DR. ROSE: That is right.

MODERATOR MC DERMOTT: *Do you agree with that, Dr. Rogers?*

DR. ROGERS: I would take issue with this, Dr. Rose. You and I have argued this at a recent meeting here at the Academy. I believe that real influenza virus infection produces a very characteristic picture, that it can be mimicked by other diseases, but which is often as characteristic as the syndrome of pneumococcal pneumonia. I would describe influenza very much as Dr. Rose has, weighting the following points, that this is an illness in which people go from good health to prostration in as short an interval as 24 hours. They have maximal height of fever within the first 24 hour period. The presence of a cough, occasional nose bleeds, all fit together into a clinical syndrome which can be differentiated as adequately as other clinical syndromes that are identified in medicine.

MODERATOR MC DERMOTT: *Are you not saying that the complete picture of the influenza syndrome is identifiable and Dr. Rose, while not apparently dissenting from that point of view, makes the point that in addition to the complete classic picture there are innumerable gradations from that to a stage of subclinical illness?*

DR. ROSE: That, in general, states the case. I would however take issue with Dr. Rogers to some small extent. I am quite certain that I have seen patients who presented an authentic clinical picture of what he would call typical influenza who did not have influenza but rather an infection with type 4 adenovirus.

DR. ROGERS: It is important to point out that Dr. Rose has seen vastly more viral infections than I have, and his point of view is to be more heavily weighted than mine!

DR. KILBOURNE: I am topographically in the middle of this panel.

My position on this point is ideologically also somewhat in the middle. I have always believed that given all the concomitants of an influenza outbreak—which of course include an actual outbreak—the diagnosis is easy in such a situation. I think when you consider an individual case, out of the context of an epidemic and the concurrence of other cases—then you do run into difficulties.

MODERATOR MC DERMOTT: That is seen every year. When there are cases of influenza exclusive of an epidemic, much depends upon the practitioner's experience.

DR. KILBOURNE: There is no doubt of the existence of inter-epidemic influenza, which we document serologically. It is unlikely, however, that much of this contributes to manifest disease in the inter-epidemic period.

MODERATOR MC DERMOTT: The more recognizable disease occurs during an epidemic; in these circumstances influenza is less likely to be confused with disease due to the other viral agents.

DR. ROGERS: I would suspect that is so. I would further make the point that difficulties in diagnosing severe influenza lie in confusion with bacterial pulmonary infections. In the course of a new epidemic there may be a problem in differentiating our friend streptococcal pharyngitis.

I would like to ask Dr. Rose whether he feels that the presence of cough suggestive of tracheitis aids in differentiating adenovirus infections from the flu syndrome, or is this too fine a point?

DR. ROSE: I don't think so, from the statistical point of view, but the practicing physician is not dealing with a statistic. He is dealing with a patient and most of the time he is encountering this patient as an example of sporadic, acute respiratory infection. We don't have many broad scale outbreaks of viral infection in the adult civilian population aside from influenza, and influenza does not appear in epidemic form very frequently, at least it has not so far.

MODERATOR MC DERMOTT: *Would you just clarify that point, Dr. Rose? You say that we don't very often have upper respiratory infections, in numbers, on a broad scale, in the absence of an influenza epidemic?*

DR. ROSE: I didn't mean in that sense, Dr. McDermott. I am sorry. I was guilty of inaccurate talk. I was thinking of this in terms of etiology. We don't have broad scale outbreaks caused by a single etio-

logical agent. What the practitioner sees, particularly during the cold months and during the spring, is a great increase in the incidence of non-bacterial infections of the upper respiratory tract, caused by a variety of viral agents. Occasionally there will be a major outbreak of a definitive illness caused by a single etiological agent, typically in the case of an influenza epidemic.

MODERATOR MC DERMOTT: *How about the situation though, when one hears talk from both physicians and the general public to the effect that there is "something going around?" That is part of our every day experience.*

DR. ROGERS: Actually, in analyzing situations of this sort, we have not as yet applied the tools of the laboratory to a sufficient extent to permit us to say with any confidence what many of these are caused by. In all likelihood within the next few years we shall be able to answer the question you put to us with a good deal more confidence than we can at the moment.

MODERATOR MC DERMOTT: *The thing happens very quickly and subsides more quickly than the tools in the laboratory can be properly employed—is that it?*

DR. ROSE: That is right. Not only that, but unfortunately the facilities for undertaking an investigation of outbreaks of this sort have not yet been developed on a sufficiently large scale to enable us to investigate all of the outbreaks we should like to.

MODERATOR MC DERMOTT: *Is it fair to say that in the absence of known influenza epidemics a variety of infectious diseases of the upper respiratory tract are seen, almost all of them caused by different viruses, some of which are identified now as the adenoviruses and some of which are unknown to us; then when these vague "something going around" occur they all may well be one virus of the adenovirus or some other group, but at this point we are unable to identify or classify them, is that it?*

DR. ROSE: That is a fair representation, I think. In the present state of our knowledge, considering the sort of infection we are discussing in the adult population, if all the laboratory tools were applied to a study of all cases of non-bacterial upper respiratory infection occurring in a community during the usual respiratory disease season, we might be able to establish the etiology in approximately 50 per cent. We should still be unable to diagnose the other 50 per cent since these

infections are caused by agents not yet isolated and identified.

MODERATOR MC DERMOTT: *And are therefore untreatable with antimicrobial drugs?*

DR. ROSE: As far as I know.

MODERATOR MC DERMOTT: *There will be a period for answering of questions submitted from the floor and I shall organize them as we go along. Could you answer some questions on complications?*

DR. ROSE: May I say one thing before we get to the questions, Dr. McDermott? Perhaps this is reiteration, but I think the practicing physician is confronted with an extremely difficult situation in connection with attempting to appraise infections of the sort we are discussing because a variety of known viral agents can cause essentially the same clinical syndrome in the human being.

MODERATOR MC DERMOTT: *They all look alike?*

DR. ROSE: They all look alike. In addition, the same viral agent may produce different clinical syndromes in man, varying not only in severity but also in character. Let us say with respect to the variance in character, that in some instances there may be involvement of the upper respiratory tract alone, and in others involvement of the lung as well. The practicing physician is then stymied for want of a definitive diagnosis and he must treat these patients symptomatically, noting the exceptions that we have already made wherein bacterial infection may play a role. In this connection it probably is just as well that no specific therapeutic measures have thus far been developed for the management of these varied viral infections, since if this were so, and if specifics were available for some of them, the physician would be in a quandary. Having a therapeutic instrument at his disposal he would be hard put to know when to use it and when not to use it.

MODERATOR MC DERMOTT: *Fortunately, all he now has to worry about are complications of the lung or those arising as the result of pharyngitis. Would you agree with that, Dr. Rogers?*

DR. ROGERS: Yes, I would.

MODERATOR MC DERMOTT: *What complications of the upper respiratory infections do you observe frequently?*

DR. KILBOURNE: May I interrupt?

MODERATOR MC DERMOTT: Yes.

DR. KILBOURNE: I want to maintain my middle of the road position on severity.

MODERATOR MC DERMOTT: The moment I heard you in the middle of the road I lost interest.

DR. KILBOURNE: Only to say that this is a constant source of recurrent amusement to me, although it should not be amusing that we have an influenza epidemic. When influenza does occur in a community (and fortunately it does not appear too often in our own general community), there is repeated and recurrent surprise on the part of the public and the physicians about its severity which leads to all sorts of speculation as to whether it will approximate in intensity the epidemic of 1918. I think this one fact does illustrate, to me at least, that perhaps there may be a melange of viruses, of the myxovirus-adenovirus types that are not identifiable, one from the other on the basis of the clinical pattern, but I do think it would be a mistake not to make an effort to distinguish from other viral infections this syndrome of influenza with its high fever, aching and prostration, tracheitis and cough. This is not the common cold, not a scratchy throat that lasts for a couple of days. It may be in some of its minor manifestations. For all practical purposes it is not, I would like to reiterate.

I apologize for interrupting. I did so because I think this point has real validity in evaluating treatment of patients. We can ignore most of the potpourri of miscellaneous infections but it would be unwise not to make an attempt to make some clinical distinction between this syndrome of influenza and that of the other group of endemic viruses.

MODERATOR MC DERMOTT: *Now that you are a man with a cause, how do you feel about this question: On the treatment of complications, do you take the position that most or some of these upper respiratory infections of this great group of viruses about which we are just beginning to learn, can cause this severe illness which is more apt to resemble influenza? Does that disease in itself mean that you would administer antimicrobial drugs? What are the complications that would cause you to administer antimicrobial drugs?*

DR. KILBOURNE: I would definitely not administer antimicrobial drugs on the basis of this diagnosis alone, regardless of the severity of the case.

MODERATOR MC DERMOTT: *To prevent complications?*

DR. KILBOURNE: Not to prevent complications. On the other hand, if the patient presented with what might be termed an incipient complication in that he showed manifestations of pulmonary involvement—

MODERATOR MC DERMOTT: Rales in the lung.

DR. KILBOURNE: Rales in the lung.

MODERATOR MC DERMOTT: *Ronchi in the bronchi?*

DR. KILBOURNE: Ronchi if you will, although I am not sure in each individual case. I would then administer an antibiotic. I think this would give me pause.

MODERATOR MC DERMOTT: *Would you agree with that, Dr. Rogers?*

DR. ROGERS: Yes, it seems to me this is an important point. I was amused by your question, "even to prevent complications?" I think it is perhaps worth stating my own point of view here, namely, that the use of antimicrobials in viral illnesses including influenza, has not proved successful in "preventing bacterial complications". I don't think you do prevent bacterial complications.

MODERATOR MC DERMOTT: *In other words, you can't do it even if you try?*

DR. ROGERS: I think there is increasing evidence to indicate that you cannot prevent the complications and consequently I am inclined to play it as does Dr. Kilbourne. I look for bacterial complications and treat if I find them present. In influenza I am concerned by the presence of any findings that suggest parenchymal lung infection.

MODERATOR MC DERMOTT: *When you talk about complications, I assume you are talking about pneumonia. What is your opinion on otitis media, sinusitis?*

DR. ROGERS: It applies. We are all aware that viral infections in children may plug off the ears and develop bacterial otitis or sinusitis. Patients with measles get pneumonia, etc., nevertheless I am quite firmly convinced that we do not prevent bacterial complications by treatment of the uncomplicated disease with antimicrobials.

MODERATOR MC DERMOTT: *Uncomplicated viral disease?*

DR. ROGERS: Uncomplicated viral disease.

MODERATOR MC DERMOTT: *You would treat mastoiditis that is severe?*

DR. ROGERS: I treat if there is any indication that a bacterial complication has occurred.

MODERATOR MC DERMOTT: *You are not too hopeful?*

DR. ROGERS: I am hopeful of treating the bacterial disease once it has arisen.

MODERATOR MC DERMOTT: *But you are not hopeful you can prevent its arising?*

DR. ROGERS: I am certain that I cannot.

MODERATOR MC DERMOTT: *You agree, Dr. Rose?*

DR. ROSE: I certainly do. I feel strongly about this point, since it has been fairly well established in a number of well controlled studies that the incidence of bacterial complications may actually be increased rather than diminished by the indiscriminate use of antibiotics for so-called prevention of secondary bacterial infection.

MODERATOR MC DERMOTT: *Upper respiratory infections that are presumably viral?*

DR. ROSE: Yes.

MODERATOR MC DERMOTT: *Do you hold with that, Dr. Kilbourne?*

DR. KILBOURNE: I do. Personally I think that the attention of the group should be brought to the studies of some who would dissent from this point of view; although Weinstein showed that in measles he could not forestall complications, there have been some studies that originally were initiated at Willard Parker by Karelitz. Those are the ones I am thinking of in which there was some suggestion that the administration of Aureomycin in measles would prevent the bronchopneumonia. However, this is hardly *upper* respiratory tract disease in children of the age group he was dealing with because many of these children have evidence of parenchymal lung involvement or of bronchiolitis, on x-ray.

MODERATOR MC DERMOTT: Let us limit the question to the adult with upper respiratory infections, presumably viral.

DR. ROGERS: Then I would wholeheartedly agree.

MODERATOR MC DERMOTT: *So, in the opinion of the panel, there is very little reason to use antimicrobial drugs for upper respiratory infections, all of which, except streptococcal, are viral in origin. Antimicrobial drugs should not be used in upper respiratory infections either to treat them or to prevent them. Complications are treated as they arise. You treat sinusitis. You treat otitis media. Would you treat otitis with antimicrobials even if you thought it arose from a viral infection?*

DR. ROSE: Without evidence of bacterial complications?

MODERATOR MC DERMOTT: Yes.

DR. ROSE: By no means.

MODERATOR MC DERMOTT: *How do you feel, Dr. Rogers?*

DR. ROGERS: I am still focussing on the adult. I feel that most of the complications seen in adults have been bacterial. I would be interested in Dr. Rose's point of view on that. In other words, when we have

seen a bulging ear drum in an adult, I have generally assumed that this is a bacterial complication and have used antibiotics.

MODERATOR MC DERMOTT: *Perhaps I had better phrase it this way: In the presence of a complication, is the distinction between a viral and a bacterial infection a problem, Dr. Rose?*

DR. ROSE: I think it is to some extent.

MODERATOR MC DERMOTT: *In adults?*

DR. ROSE: Yes. However, I think that one would normally not administer antibiotics to patients in circumstances where there appeared to be no evidence of a bacterial complication. Indeed, you are asking for trouble if you give antibiotics.

DR. ROGERS: That is a very important point. One so often hears the phrase, "I know he does not have any infection but I would certainly sleep better if he were on antibiotics".

MODERATOR MC DERMOTT: "It cannot do any harm."

DR. ROGERS: This is a snare and a delusion. Our thinking has gradually come full circle. We first thought antibiotics might prevent bacterial infection, then that they at least did no harm. Now, as Dr. Rose pointed out, there is definite evidence that one can increase the bacterial complications in certain viral infections. Further, these complications are often due to organisms that are difficult to treat. Instead of pneumococcal or streptococcal infections, one is confronted with the problem of dealing with pseudomonas, staphylococcal or fungal infections.

MODERATOR MC DERMOTT: *How about the complications of an upper respiratory tract, presumably viral in origin? How about the pneumonic complications that seem to be viral in origin? Dr. Rose mentioned that sometimes these processes extend downward and cause a pneumonia. How about the treatment in such cases? The clinician is faced with the patient who has had the upper respiratory infection now followed by definite evidence of involvement of lung parenchyma.*

DR. ROSE: Certain viral infections of the lung do, of course, respond to antimicrobial therapy. Perhaps the best examples are those caused by viruses of the psittacosis-ornithosis group.

MODERATOR MC DERMOTT: *How often does one see them?*

DR. ROSE: This kind of infection is seldom seen in this country.

MODERATOR MC DERMOTT: *Only a very small percentage of the total number of patients you might see with the syndrome of viral pneumonia?*

DR. ROSE: The chances that a practitioner will see a patient with this type of infection are virtually nil. The same thing would obtain, in this part of the country at least, for certain rickettsial infections, such as Q fever, which also respond to broad-spectrum antibiotics. The mere fact that such infections exist would by no means be a reason for administering antimicrobial agents to anyone who had what appeared to be a so-called viral pneumonia. There is some difference of opinion as to whether classical primary atypical pneumonia, which is caused by an unidentified virus or group of viruses, may respond to some of the broad-spectrum antibiotics, particularly drugs of the tetracycline group. I myself believe that if the diagnosis is reasonably certain in these individuals, one of the tetracyclines ought to be given, but I am quite sure that other members on this panel would disagree with that point of view and in all likelihood they would have a perfectly valid reason for doing so. In the case of the other viral infections there would really be no point in using antimicrobials, because there is no evidence that any of the viral infections respond specifically to them. Influenza is an example. Adenoviral infections of the lung, incidentally, may be very extensive both in adults and in children.

MODERATOR MC DERMOTT: *And look like primary atypical pneumonia when you see it?*

DR. ROSE: Yes, the pulmonary involvement may be extensive and occasionally cause death in children. In a few instances such infection actually has caused death in adults. It does not respond to antimicrobial agents.

MODERATOR MC DERMOTT: *With an influenza viral infection do you have involvement of the lung? How do you know the involvement of the lung is viral?*

DR. ROSE: You have to make the assumption, and you test that assumption by obtaining appropriate specimens to see whether there is evidence of secondary bacterial infection.

MODERATOR MC DERMOTT: *Do you think you can do it on clinical grounds?*

DR. ROSE: I don't think so.

MODERATOR MC DERMOTT: *Do you think you can get any hints?*

DR. ROSE: Yes, I do.

MODERATOR MC DERMOTT: *Because there is no time, things happen fast?*

DR. ROSE: I believe the character of the sputum in these individuals is frequently a helpful sign. The patient has evidence of pneumonitis under the circumstances we are discussing and if the sputum is merely mucoid or glary, and if the white count is within normal limits, the chances are that the patient does not have a bacterial pneumonia at that point. If, on the other hand, the sputum is mucopurulent, copious or bloody, and if there is a sharp increase in the white count, I think one has to make the assumption, without waiting for any laboratory procedures, that there may be a secondary infection and treat accordingly. *However, before antimicrobial therapy is begun one should certainly examine the sputum by smear and also obtain a specimen for culture.*

MODERATOR MC DERMOTT: *Is the tendency more to treat, or not to treat, if the diagnostic evidence is inconclusive?*

DR. ROSE: If inconclusive, which means that there is a reasonable possibility of bacterial infection, I think in most instances the physician would be wise to institute therapy and be guided thereafter by the results of the laboratory examinations.

MODERATOR MC DERMOTT: *Dr. Rogers, how do you treat the patient with presumably a viral infection and presumably the moderately extreme or extreme forms of what might be called the influenza syndrome when that patient develops rales in the lungs or some evidence of pulmonary involvement?*

DR. ROGERS: I would have to separate such patients into two groups. Let us consider the non-influenzal viral infections first. I would concur with what Dr. Rose says. I am inclined not to treat the classic case of primary atypical pneumonia with antibiotics.

MODERATOR MC DERMOTT: *Do you feel strongly about it one way or another?*

DR. ROGERS: I don't feel strongly about it. The specific viral pneumonias of the psittacosis-ornithosis group are clinically indistinguishable from primary atypical pneumonia. My rule of thumb has been that people with psittacosis look sicker and have higher temperatures. So when patients with the syndrome of atypical pneumonia have temperatures over 104° and are sick, I treat them.

MODERATOR MC DERMOTT: *How about palpation of the spleen? Is that of any help?*

DR. ROGERS: I have not found it to be of help. I have not felt the spleens in very many of these patients.

If I may go on to the influenza group, here my practice has been somewhat different than that of Dr. Rose's. In examining patients with influenza I have been impressed with the fact that only very few of them show any evidence of parenchymal lung involvement, on x-ray or in the presence of rales.

MODERATOR MC DERMOTT: *Only a small group, a minority?*

DR. ROGERS: In the Bellevue Emergency Room in the recent epidemic (1957), I think about two patients out of every 100 demonstrated rales. It seems to me that it is more common to have a bacterial infection of the lung than a viral one in influenza. As you well know, these can proceed so swiftly that I am inclined to treat on the assumption that it is bacterial infection when pulmonary findings are present in patients who have the influenza syndrome.

MODERATOR MC DERMOTT: *To summarize your position: For most patients with an upper respiratory infection that appears viral in origin but is not the influenza syndrome, you don't treat when they develop pulmonary complications. On the other hand, if the pulmonary complications are severe, you treat and should the pulmonary complications occur in a setting believed to be viral influenza, you treat because they are more apt to be bacterial?*

DR. ROGERS: Right. In this category the pulmonary complications are severe. I do this only in the attempt to pick them up.

MODERATOR MC DERMOTT: The odd case.

DR. ROGERS: The possible case of psittacosis that might slip by because I cannot differentiate it from atypical pneumonia.

MODERATOR MC DERMOTT: *Dr. Kilbourne, to switch the question, do you think we are going to have problems with influenza this year (1958)?*

DR. KILBOURNE: Could I first comment briefly on the last issue? I think Dr. Rogers is ignoring some of his own evidence that he and I gathered last year, in weighting the decision to treat or not to treat in the presence of influenza complicated by pulmonary involvement. In looking over some of our data, we concluded that, in general, if there was secondary bacterial involvement this became manifest from the clinical picture of bacterial pneumonia over and above any aching from the influenza.

MODERATOR MC DERMOTT: *The typical bacterial pneumonia picture?*

DR. KILBOURNE: A high incidence of pain in the chest; the character

of the sputum, as Dr. Rose mentioned, was useful; the leukopenia sometimes seen with flu did not prevent the leukocytosis usually associated with bacterial infection, so this guide was not lost. I think, therefore, that one has the useful guides of just looking for a diagnosis of bacterial pneumonia directly.

I also had a footnote about primary atypical pneumonia. I have been searching for it in vain for about five or six years.

MODERATOR MC DERMOTT: *Where has it gone?*

DR. KILBOURNE: I remember the virus symposium held in Detroit about three years ago. A group of people from all over the country were polled informally and none had seen the cold agglutinin-positive disease.

MODERATOR MC DERMOTT: The clinical syndrome accompanied by serological test.

DR. KILBOURNE: I wonder whether at the moment we have to be too concerned with this entity and I would be interested to hear Dr. Rose's statements on the incidence.

MODERATOR MC DERMOTT: *Dr. Rose, has that been your experience? You have not seen much lately?*

DR. ROSE: I think it has been generally true throughout the country, as a matter of fact throughout the world. However, the disease does continue to occur sporadically.

MODERATOR MC DERMOTT: It occurs in waves or has occurred in waves.

DR. ROSE: One of the interesting things about so-called classical primary atypical pneumonia is that one is apt to see it in the summer time, which is something the clinician might well bear in mind.

MODERATOR MC DERMOTT: We used to call it "summer pneumonia" when we were students.

I am going to switch now to questions from the floor, one of which I will address to Dr. Kilbourne. The question is: What likelihood, if any, is there of an outbreak of Asian influenza in epidemic proportions this winter and should preventive measures be taken?

DR. KILBOURNE: Again one has to get out the crystal ball. I think it is perfectly reasonable to assume that there will be influenza this winter, that it will be of the same immunological strain encountered last winter, that it will be far less in extent than was seen last winter and will probably occur in scattered sporadic outbreaks, but I should be very

surprised indeed if it does not occur.

MODERATOR MC DERMOTT: *You think each physician will see one or more patients?*

DR. KILBOURNE: This statement is based on the evidence that we have from some limited serological investigations of populations that were visited by the disease last winter, which would indicate that the attack rate was far from 100 per cent in some localities and in some localities it was as low as 20-30 per cent. This means there is a reservoir of susceptible people who may still possibly be infected with the same agent even if the virus does not change antigenically.

MODERATOR MC DERMOTT: *So our conversations about what to do with complications of the viral influenza syndrome are not academic?*

DR. KILBOURNE: I don't think they are. To answer part two of your question, as to whether any wide scale immunization program should go on, my personal feeling on this is that as the Surgeon General proposed originally at the start of the last outbreak, certain high risk groups might be immunized and preferably immunized with the polyvalent vaccine now available which includes not only the Asiatic strain but older A types and also influenza B. Although I don't feel very strongly about this point, it seems to me that nothing is to be lost by such an immunization procedure.

MODERATOR MC DERMOTT: *Done by the calendar, not awaiting the actual outbreak?*

DR. KILBOURNE: I think it should be done now (October).

MODERATOR MC DERMOTT: That is what I mean. In order to be sure to cover all the questions, I am going to ask the members of the panel to declare their dissents and silence will be taken to mean reasonable concurrence.

The second part of the question has to do with the white count with respect to antimicrobial therapy. That has been covered.

The next question: Is hypoglobulinemia a factor in making an individual vulnerable to repeated upper respiratory tract or viral infections? How can this be corrected in the adult?

DR. ROGERS: I don't believe that it is. I think we continue to widen our search for host factors that might explain susceptible people. It is clear that the children with agammaglobulinemia can have repeated episodes of viral disease. One of the interesting features is that such disease looks like viral disease in anybody else. If they have measles they

get well in the same period of time, etc. I would guess that gamma globulin plays no particularly important role in recovery from viral infection. Would you agree with that, Dr. Rose, or am I sticking my neck out too far?

DR. ROSE: I would certainly agree to a large extent, provided, of course, that you confine yourself to viral infections.

DR. ROGERS: I am speaking only of viral infection.

DR. ROSE: Bacterial infections are quite another matter.

DR. ROGERS: An important point.

MODERATOR MC DERMOTT: *Bacterial infections would be much more susceptible. Is antibiotic treatment indicated in acute infectious bronchitis in adults? That is a sufficiently precise question. Would you express yourself on that, Dr. Rose?*

DR. ROSE: This depends upon the etiologic agent.

MODERATOR MC DERMOTT: *You would say what you said before?*

DR. ROSE: Acute infectious bronchitis may be a pneumococcal infection. In that instance it certainly ought to be treated with antimicrobials.

MODERATOR MC DERMOTT: *In any adult, this is rare?*

DR. ROSE: Very rare.

MODERATOR MC DERMOTT: *But it happens?*

DR. ROSE: It happens.

MODERATOR MC DERMOTT: *Staphylococcal?*

DR. ROSE: Very rare.

MODERATOR MC DERMOTT: *What would you say is the origin of most acute bronchitis in the adult?*

DR. ROSE: Most acute bronchitis in adults which does not go on to the development of pulmonary complications is viral in origin.

MODERATOR MC DERMOTT: *Is viral, but if pulmonary complications are present then you may be dealing with a bacterial pneumonia, bronchial. Does the panel agree if the original 17 year old boy with bronchitis was found to have hemolytic coagulase-positive staphylococci in the throat culture they would treat with an appropriate antibiotic such as novobiocin, Dr. Kilbourne?*

DR. KILBOURNE: I would not.

MODERATOR MC DERMOTT: *Dr. Rogers?*

DR. ROGERS: I would not.

MODERATOR MC DERMOTT: *You feel strongly?*

DR. ROGERS: That is an important question because it arises so frequently. I think the more we know about staphylococci the more frightened we become about them, but I also think it is increasingly clear that they are of no pathologic significance in the great percentage of cases where they are found. It is a very common finding to get coagulase-positive hemolytic staphylococci out of red throats. I am equally convinced they play little or no role in the red throat, with occasional exceptions. Staphylococcal pharyngitis is a disease entity but a very rare one.

MODERATOR MC DERMOTT: *In the 17 year old boy. If it were a two year old child?*

DR. ROGERS: Here I would be more suspicious of the staphylococcus as the etiologic agent.

MODERATOR MC DERMOTT: *In a 61 year old woman with diabetes, insulin treated?*

DR. ROGERS: I would keep her off the antibiotics.

MODERATOR MC DERMOTT: *Does the panel agree? All agree!*

What is the reaction of the panel to the value of viral vaccines? By that I suppose not only vaccines against influenza are meant but the vaccines we have been reading about against the adenovirus. Dr. Rose?

DR. ROSE: I think the subject has been covered, at least in part, by Dr. Kilbourne with respect to immunization against influenza. The usefulness of adenovirus vaccines has not been very well delineated so far except in certain military populations. There isn't any question that adenovirus infection is common in infancy and childhood because most adults have circulating antibodies.

MODERATOR MC DERMOTT: *It is a problem in children and the young adult?*

DR. ROSE: One has to assume that all children have been infected at some time with adenoviral agents. There is, however, very little evidence that adenoviruses cause broad scale outbreaks of respiratory infection in children. At least such evidence has not been forthcoming up to the present time. My own feeling is that this type of vaccine should not be administered routinely to children because I fail to see just what the reason might be for using it.

MODERATOR MC DERMOTT: *The illness is not very severe?*

DR. ROSE: The illness in the child ordinarily runs an uncomplicated course. The child recovers and as he gets on into later life retains

some degree of resistance against further infection with members of this group. My own feeling is that it would be a mistake to use this particular type of vaccine on a broad scale in infancy and childhood. There are certain people who would probably disagree with this point of view because, as has already been pointed out, there have been deaths in infants caused by adenoviruses, particularly Type 1 adenovirus. Whether this actually constitutes an indication for the administration of vaccine is still open to question.

MODERATOR MC DERMOTT: *Does the panel agree with that? There is no point in using vaccine for the adenovirus infections in civilian practice? Everyone agrees!*

The next question is related. Do adenoviruses predispose to secondary bacterial infection or do they cause tonsillar node enlargement?

DR. KILBOURNE: It has been surprising, particularly in the well-studied military outbreaks, that so little secondary bacterial infection follows adenovirus infection. However, I would have the same reservation that Dr. Rose apparently has about the lack of adequate clinical delineation of these agents as they go through a normal community. I think most of our studies have been limited.

MODERATOR MC DERMOTT: *To a closed group?*

DR. KILBOURNE: To a closed population group under special conditions.

MODERATOR MC DERMOTT: *So you would not favor vaccination?*

DR. KILBOURNE: No, except in the obviously important situations in the military or in any institutionalized young adults.

MODERATOR MC DERMOTT: *How about the lymph node enlargement?*

DR. KILBOURNE: Lymph node enlargement does certainly occur.

MODERATOR MC DERMOTT: *Dr. Rogers, many patients recovering from influenza cough green purulent sputum. Is this secondary bacterial bronchitis? If so, does this require treatment?*

DR. ROGERS: I think this is an important question. I am not sure that I know the answer. Certainly one can culture organisms out of the residual bronchial secretions that some patients have. I believe that this represents the biologic process of the viral infection, which can denude the tracheal bronchial tree leaving a very purulent secretion which is not infected with bacteria.

MODERATOR MC DERMOTT: *It does not require treatment?*

DR. ROGERS: I have, in general, not treated those. If patients have continued to cough up large amounts of purulent sputum from which I can culture organisms, I have sometimes empirically treated. I am not convinced it has changed the course of the disease.

MODERATOR MC DERMOTT: *How would you feel if the patient had several attacks of asthma in this situation?*

DR. ROGERS: I might broaden your query. I think if any underlying chronic pulmonary disease exists, I would treat it with antibiotics much more quickly.

MODERATOR MC DERMOTT: *An otherwise healthy adult with this situation you would not, or an otherwise healthy child you would not?*

DR. ROGERS: No.

MODERATOR MC DERMOTT: *Please comment on the value of tonsil-adenoidectomy in repeated upper respiratory tract infections, first in children and then in adults. Dr. Rose?*

DR. ROSE: I don't think it makes the slightest difference. I certainly would not perform the operative procedure in trying to prevent this sort of complication because I don't think there is any causal relationship.

MODERATOR MC DERMOTT: *Do you believe that a child who has had repeated infections may "outgrow" that phase?*

DR. ROSE: I am not quite certain that he will. I think in some instances the bulk of adenoidal tissues and the size of the tonsils may impose mechanical difficulties, in which circumstances it is occasionally proper to perform this operation in order to relieve obstruction to breathing, but I cannot see any other valid reason for it.

MODERATOR MC DERMOTT: *Not with the intention of prevention of disease? Do you agree, Dr. Rogers?*

DR. KILBOURNE: Yes.

DR. ROGERS: We seem to be a group of therapeutic nihilists!

MODERATOR MC DERMOTT: *You are sympathetic to the problems though?*

Some one asks: In the original case, Dr. Rose, you mentioned an abnormally high leukocyte count, 15-18,000. It would be helpful in pointing your attention toward your degree of conviction towards streptococcal disease. The questioner asks whether the pulse rate would be of any help in that situation.

DR. ROSE: I should not think so.

MODERATOR MC DERMOTT: *Does the panel agree?*

DR. ROGERS: I would agree. The pulse rate may be either normal or increased.

DR. ROSE: I would not know where to draw the line.

DR. KILBOURNE: I think that question probably is introduced because of a "truism", which I don't think is a truism, that you get a bradycardia with viral infections, period. I would dissent from that, so I would agree with Dr. Rose.

MODERATOR MC DERMOTT: You would agree with Dr. Rose.

Dr. Rose mentioned the rare situation of pneumococcus causing bronchitis. The question is: Does pneumococcus cause any upper respiratory tract infection, Dr. Rogers?

DR. ROGERS: No.

MODERATOR MC DERMOTT: *Including Dr. Rose's?*

DR. ROGERS: I think for practical purposes, and I mean infections above the neck, no.

MODERATOR MC DERMOTT: *You would agree that it is very rare in the bronchi?*

DR. ROGERS: Secondary complications in the ear yes, but pharyngitis or upper respiratory problems, no, I don't believe so.

MODERATOR MC DERMOTT: *But it can cause sinusitis secondarily?*

DR. ROGERS: Yes.

MODERATOR MC DERMOTT: *Would you agree?*

DR. ROSE: It not only can, but frequently does.

MODERATOR MC DERMOTT: *But not a primary cause of upper respiratory?*

DR. ROSE: No.

MODERATOR MC DERMOTT: *Mention should be made of epidemics of* ECHO *virus infections, especially Type 9, which may definitely cause types of upper respiratory infections. Dr. Rose, do you concur?*

DR. ROSE: There are other ECHO types that have been associated with upper respiratory infections. Generally speaking, from what little we know about ECHO virus infections at the moment, they not infrequently have a gastrointestinal component associated with them, so that in addition to the acute upper respiratory symptoms there may also be evidence of an acute enteritis.

DR. ROGERS: And rash.

DR. KILBOURNE: And also, Dr. Rose, would you agree with some of

the data being accumulated which appear to indicate that adenoviruses in children may cause at least some diarrheal involvement? Do you think that is so?

DR. ROSE: I am not certain on that point, Dr. Kilbourne. I have had no experience with it.

MODERATOR MC DERMOTT: *The laity stoutly maintain and the virologists stoutly deny that an upset gastrointestinal tract can result from a viral infection. Is that true?*

DR. ROSE: That is true. Actually we have examined a moderate number of fecal specimens for the presence of adenovirus in persons who have had gastrointestinal manifestations, particularly in young persons with so-called acute mesenteric lymphadenitis. We have been completely unsuccessful so far in obtaining adenovirus from the feces.

DR. KILBOURNE: We have had a similar, but very limited, experience. Dr. McDermott, in line with that question, it should be pointed out that we have not touched on many viruses responsible for upper respiratory infection, including the Coxsackie group, notably the Group B type, also a rare one which causes primary pharyngitis, which could mimic the case of the boy you gave us earlier, primary herpes simplex infection in an adult.

MODERATOR MC DERMOTT: *The next question: What are the types of adenovirus and how may they be differentiated? Dr. Kilbourne, is it fair to say that for years the laity, when they had respiratory infection, have been going around saying they "had a virus"? There is no evidence, of course, of a virus. Nobody looked for virus. If they looked they did not have the means of finding them, so the concept has developed, both in the profession and the laity, that there are a certain number of upper respiratory infections which, as you all have said, are viral in origin. Since 1933, we have been able to isolate one influenza virus, and two or three more since then. Now, is it not true that in terms of practical wisdom or practical knowledge necessary for the treatment of the patient, that all this talk about adenoviruses,* ECHO *viruses, this or that kind of virus, is merely an indication that our laboratory and scientific proficiency is beginning to identify these things and may really indicate the possibility of grouping them together as an aid to the physician in dealing with these problems?*

DR KILBOURNE: In general, that is true, Dr. McDermott. It is an over-simplification. I think with increased laboratory proficiency and

better diagnosis that there are some spillovers into the clinical areas. For example, we now know that adenoviruses are responsible for conjunctivitis. This is an example of a clinical link that can pull some cases together.

MODERATOR MC DERMOTT: *We are now in the phase of taking these viruses, which at the moment have no more practical value than the old patient's idea "I have a virus", and beginning to associate a few clinical manifestations here and there and perhaps some day more will become apparent, is that it?*

DR. KILBOURNE: That is it.

MODERATOR MC DERMOTT: For practical purposes, then, the panel, perhaps with Dr. Rose dissenting, wishes to make a crude differentiation between the worst cases of the influenza syndrome and the rest, with the rest representing this large group of viruses which, in clinical terms, all represent much the same problem.

DR. ROSE: I don't think I would dissent from that in the way it was phrased.

MODERATOR MC DERMOTT: Your point is that they merge rather than drop off precipitously, one and then the other.

"If, as it is assumed, that the practical disappearance of mastoiditis and radical sinus operative procedures are due to the use of antibiotics, especially penicillin, how could the panel ignore the value of antibiotics as prophylactic agents against complications?"

I really address that question to Dr. Rogers. Do you mean that you would not believe you can prevent mastoiditis or otitis in streptococcal infections? This man definitely thinks you can prevent mastoiditis and otitis.

DR. ROGERS: I think he has an important point that we did not get across. We do not prevent bacterial complications of *viral* disease by the use of drugs. We very definitely can prevent suppurative complications of *bacterial* infections.

MODERATOR MC DERMOTT: *Bacterial complications of bacterial diseases!*

DR. ROGERS: When faced with obvious bacterial infection of the ear, we can prevent mastoiditis and do.

MODERATOR MC DERMOTT: As a matter of fact, this was accomplished with the sulfonamides, starting with sulfanilamide. We did not have to wait for penicillin.

This question requires a rather extensive answer:

"Should antibiotics be given to adults with bronchitis complicating viral infection with purulent sputum, with possible bacterial infection?

Dr. Rogers answers that with the green sputum point.

Should serious pneumococcal infections be treated for ten days like the streptococcal, in order for full, natural resistance to appear?

I would take it that a patient with pneumonia is meant, how do you feel about that, Dr. Rogers?

DR. ROGERS: That is a good question. I feel that pneumococcal disease, regardless of its seriousness, should probably be treated beyond eight or nine days of the disease process. In other words, if the patient is first seen on day 6, I think it is perfectly reasonable to treat for three or four days and stop.

MODERATOR MC DERMOTT: *Day 6, after the pain in the chest of pneumonia?*

DR. ROGERS: Absolutely. I believe it is probably important to treat beyond the period of the antibody response. It has been shown that if the patient with pneumococcal pneumonia is treated from day 1 until afebrile and then treatment is stopped, he can have a classical relapse with classical pneumonia. I thus think that treatment should be continued for ten days, but with this exception, if the patient is first seen on day 6 of his pneumonia you don't have to treat him as long as on day 1.

MODERATOR MC DERMOTT: Most such patients are seen on day 2, so to all intents and purposes it means treating for a week or ten days.

In a young child, 3-5 or younger, fever 104°, acutely ill, but no clear clinical symptoms, only a slight sore throat, would you give penicillin?

This is really the question of unexplained fever in a 3-5 year old child with a fever and possibly a sore throat, not much of a sore throat. How do you feel about that, Dr. Kilbourne?

DR. KILBOURNE: No.

MODERATOR MC DERMOTT: *Dr. Rose?*

DR. ROSE: I would like to ask a question first and I can put it in one word—why? If the child has an unexplained fever of 104°, if this is a bacterial infection and if the nature of the bacterial infection is not known, there is no guarantee that penicillin will be the drug of choice. As a matter of fact, the infection may be caused by an organism which

is resistant to penicillin. One might just as readily rephrase the question by saying, if we have this situation should we at once give multiple antibiotic therapy in order to cover the various possibilities? I should not administer antibiotics under this particular set of circumstances. I should want more information before starting antibiotic therapy.

MODERATOR MC DERMOTT: *Do you agree, Dr. Rogers?*

DR. ROGERS: I agree, I would want more information. I might start the drug. I think Dr. Rose is saying the same thing. His question of "why" is important. Many times we are faced with the necessity of giving drugs without a diagnosis because of possibilities that we cannot rule out.

MODERATOR MC DERMOTT: *In this situation?*

DR. ROGERS: In this situation I would ask myself a number of specific questions: Can I rule out a meningococcal infection? If I could not, many times I would feel obligated to treat.

MODERATOR MC DERMOTT: *Would you use penicillin?*

DR. ROGERS: No.

MODERATOR MC DERMOTT: *What would you use?*

DR. ROGERS: The "why" is important. I would treat for the infection that I thought the patient had. I think it is important to go through an armchair bacteriological differential diagnosis; could this be a meningococcal infection, could this be a urinary tract infection, etc.? If there are some possibilities high on the list I would treat quite specifically for them.

MODERATOR MC DERMOTT: *Dr. Kilbourne, you agree?*

DR. KILBOURNE: With what, with whom?

MODERATOR MC DERMOTT: *With Dr. Rose and Dr. Rogers.*

DR. KILBOURNE: I am a little more on Dr. Rose's side on this one. I think given this set of circumstances we essentially don't have much clinical data to determine whether it is an incipient meningococcal infection or not. I think—to restate it or to bring Dr. Rose and Dr. Rogers together in happy harmony—it would be my conviction that the most important thing in this circumstance is just careful observation—and I realize the exigencies of practice do not always make it possible to sit at the patient's bedside—but I do think most mothers are perceptive enough so that if they are told to alert you to the dangers, if you will spell out certain symptoms that worry you, they will respond. Sometimes they will make them up and sometimes they won't, but more often

than not I would not treat.

MODERATOR MC DERMOTT: *Let me put this in quantitative terms. Dr. Kilbourne, you said more often than not you would not treat. I infer that you do not feel as strongly about the starting of tetracycline therapy, for example, as you would feel about the earlier questions on bacterial complications of viral respiratory infections. The entire panel were all pretty well in opposition to it. Is that right? It is not as great a sin, so to speak?*

DR. KILBOURNE: I don't think so, for this reason: If this particular clinical situation happened today in my 5 year old boy I would treat him but I would treat him because I know his history and I know he has a tendency to bronchiolitis every time he gets an upper respiratory infection. I would not be undertaking a course of prophylaxis but I would be attempting to treat what in his particular case seems to be an inevitable bacterial infection. But the reason I introduce this point is that I think you have to particularize depending upon the patient's history.

MODERATOR MC DERMOTT: *How about steroids in severe debilitating viral infections?*

DR. KILBOURNE: I think there is a very definite place for steroids in the treatment of acute infections of all types. The limits of steroids have not been well defined. There are more dangers inherent in the use of steroids in infections than not. I am convinced that the lives of some patients with pneumococcal meningitis, for example, have been saved by ameliorating effects of steroids on the pathophysiology which involves fever and the like, but there are more dangers inherent in this than not. This can be a useful type of therapy, but, in short, it is dangerous.

MODERATOR MC DERMOTT: *Most of the viral infections in which you would use steroids are not respiratory infections, is that correct?*

DR. KILBOURNE: Specifically viral infections?

MODERATOR MC DERMOTT: *Yes, just asked in terms of viral infections.*

DR. KILBOURNE: In terms of viral infection, I have to retract and say I can think of very few instances when I would use steroids and I can think of a mass of evidence demonstrating that such diseases as varicella may be fatal if the disease occurs during the course of steroid administration. I am sorry, I was speaking largely about bacterial infections.

MODERATOR MC DERMOTT: *Not viral.*

DR. KILBOURNE: In terms of viral infections I can think of no real indication. Parenthetically, for rickettsial infections in which the toxemia may be similar to that in typhoid fever, Woodward has had good experience.

MODERATOR MC DERMOTT: *But not viral infections, I see.*

DR. ROSE: May I say one word?

MODERATOR MC DERMOTT: *Yes.*

DR. ROSE: This might be an important point in view of what Dr. Kilbourne said about varicella. I should agree that disease occurring in the course of steroid administration may be unusually severe and sometimes fatal, but there are certain types of infections, such as varicella pneumonia in adults, wherein the administration of steroids at the height of the disease may be life saving. Several examples have been published in the literature. Dr. Meiklejohn had a series of such patients at the University of Colorado. We saw a similar patient last year.

MODERATOR MC DERMOTT: *Real chickenpox?*

DR. ROSE: Varicella pneumonia in a young mother who had been in contact with her children who had the disease. I am certain that this patient would have died if we had not administered large doses of Meticorten.

MODERATOR MC DERMOTT: *Pneumonia in the presence of severe chickenpox.*

DR. ROSE: Severe chickenpox pneumonia in an adult with acute respiratory embarrassment and impending fatal issue constitutes a real indication for steroid treatment.

MODERATOR MC DERMOTT: *Any dissent from that?*

DR. KILBOURNE: I will not dissent from that. I had forgotten about those cases.

MODERATOR MC DERMOTT: We are at the end of our time. I would like to thank the members of the panel for their contributions and the audience for its sustained interest and attention.

MUSICAL CREATIVENESS AND EMOTIONAL DISTURBANCE*

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SINCE THE introduction and development of a dynamic psychiatry, interest has been focused from time to time on the creative process and on the relationship between creativeness and emotional disturbance. If it seems questionable whether the psychiatrist by means of his particular discipline can throw much light on the creative process itself, the relationship between emotional disturbance and creativity is, nevertheless, one which concerns him in a very direct sense. There is in fact a prevailing notion and even fear among creative people, who are beset with emotional disturbances, that a therapy which would be successful in relieving the disorder might also hinder the creativity. Indeed, there are a number of theoretical writings which could tend to give rise to such an attitude by their suggestion that creative expression, particularly of an artistic type, is associated with sublimation of unconscious needs or conflicts[1-6]. On the other hand, Kubie[7] has associated creativity with preconscious rather than unconscious processes and has specifically denied the theory of sublimation of unsatisfied unconscious needs as playing a role. For him neurotic disturbances have no particular relation to the creative process except that they impede it, so that the emotionally disturbed creator expresses himself successfully in spite, rather than because, of his neurosis.

Much of the psychiatric literature on this subject matter tends to deal with creativeness as a kind of general process, whether it expresses itself in the form of music, writing, the graphic arts, or scientific discovery. Undoubtedly this approach is a justified one, for surely there must be features which creative expression has in common, irrespective of the choice of medium. It is also likely that there are certain characteristics unique to each particular type of creative expression

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concerning which investigation would be fruitful. Such is the approach taken in this paper, which deals with the subject of musical creativeness and emotional disturbance. It is interesting but quite understandable that those writings which have dealt with psychologic aspects of particular kinds of creativeness have concerned themselves far more with authors, and even with painters, than they have with composers. The reason for this, which is almost self-evident, lies in the fact that in the case of writers especially, an examination of the creative product itself may reveal in quite a definite way important features in the psychology of the creator. This is obviously far less so in the case of a composer, and here we are more restricted to biographical material or to non-musical autobiographical writing or letters. Before discussing the problem of emotional disturbance and musical creativeness, it would appear necessary to review in some detail various features common to composers and to music which would justify the approach that theirs is indeed a very unique kind of creativeness and creation.

Some Observations About Composers

One is struck first of all by the fact that manifestations of musical talent (not always precocious but quite definite) appear in most composers very early in life. Indeed, in cases where great composers have failed to display evidence of such talent before the age of 12, their biographies generally note this fact as an unusual finding. Actually, the creative drive itself often seems to appear quite early in life. Most great musical creators composed in small and sometimes large forms in their teens, if not before, and in a significant number of instances were able to create masterpieces or works of more than historical interest during this period of their lives. Few people would be especially concerned with the fact that Schubert's setting of the *Erlkoenig* represented the work of an 18 year old boy. Such an example of a masterpiece of music conceived by a teenager is in fact not too unusual. Without laboring the point of whether musical creativeness asserts itself in general earlier than creativeness in other media, there is little doubt that the average great composer has clearly indicated his choice of creative expression at a time when his personality is still in a developmental stage; that he may be able, be he a Mozart or a Mendelssohn, to produce musical masterpieces before he has reached adulthood.

It should also be noted in this regard that the musical talent of

composers has often been extensively developed during childhood, principally through the study of musical instruments. Whatever the precocity of the talent, this implies a considerable preoccupation with music in the youngster, as well as a large amount of time spent upon the development of musical proficiency in place of other activities in which his playmates or contemporaries may be engaging. If we may generalize from the biographies of great composers, it is possible to say that most of those without a solid early foundation in music encountered difficulties in composing in the larger forms. But surely the early devotion to music of composers must play an important role in their psychological development and in general has no counterpart when one considers other kinds of creators. One must remember in this regard that musical training is in general not part of the educational process of the average youngster. That is to say, formal schooling, and indeed preschool education, places its greatest emphasis upon the development of verbal facility and comprehension, and to a lesser extent the visual arts. The youngster who devotes himself to the development of a musical technique is therefore definitely unusual and will stand out from the group. Whether he does this as a result of some overwhelming urge or preoccupation with the medium, or as a result of an affective detachment from his group, or in submissive response to parental pressures, such a phenomenon may be presumed to be intimately bound with his character structure and his development.

Any discussion of music as an artistic expression must note that in contrast to other arts, music has both performing and creative aspects, which are at the same time separate and intimately related one to the other. Most great composers are also musicians of relatively adequate accomplishment and some have been distinguished instrumentalists or interpreters. At the same time most distinguished performers have at some time in the course of their lives tried their hand at composing, however assiduously they may have concealed their none-too-inspired products. But these individuals generally become either primarily composers or primarily musicians. What determines this choice is essentially unknown. In the case of the composer who is also a performer, it means again that he has devoted an extraordinary measure of his time, energy, and total preoccupation in developing a command of musical expression, usually starting from childhood or adolescence.

Of passing and speculative interest with respect to distinctive fea-

tures associated with composers in contrast to other kinds of creators is the fact that there is yet to appear a distinguished woman composer. This is interesting, because in the past two centuries, as we have witnessed the gradual so-called emancipation of women, their sex has produced distinguished novelists, playwrights, painters, sculptors, and scientists. Yet, we still await a first-rate woman composer, and even second rate composers are hard to find. It is not difficult to find a distinguished instrumentalist or pedagogue among women, but the challenge of musical composition has, for some reason, not as yet been successfully met. This is all the more unusual because education of girls in the home has so often included music, at least in the European culture. In this country, in fact, the study of music among boys is oftentimes regarded as a kind of "sissified" activity, whereas it is well accepted in girls. It is therefore puzzling that whereas women have succeeded in becoming distinguished interpreters of men's compositions, they are not as yet able to create in this medium in their own right.

The Creative Musical Process and Its Psychologic Aspects

Perhaps more basic to an understanding of musical creativeness would be certain observations on the nature of music as a medium of expression. Music has often been called a language and indeed it has many characteristics to justify such a description. It possesses a similar flow. In contrast to graphic arts it requires time for its unfolding, and one must follow its own special form and logic to its conclusion before one can comprehend the whole. But if music is indeed a language, it is also a nonverbal language. It defies translation into words. By the same token, it is completely abstract and highly symbolic. With all due respect for the program notes which generally accompany our concerts, it would be very difficult indeed for a writer to describe a piece of music having its first performance, in such a way that one could conjure up an accurate musical imagery of what one was about to hear. Eventually the writer gets around to a notation of a musical theme.

There is still another distinctive feature of the musical language as it is used by the composer. By the act of creating, the composer has not communicated anything. At best he can be said to be talking to himself. For his creative expression to constitute a form of communication it must be performed, and it generally depends upon performance by others. When a painter has finished his creative product, it is there for

anyone to see it. The novelist, if only he has the good fortune to find a publisher, has, by the very act of creating, produced something that can be read and re-read without further ado. Whatever the intentions of these other artists, they have only to find an audience in order to communicate what they have felt or thought. But the composer must find a performer as well as an audience. Even if he himself is a distinguished musician, he generally gets around to writing works for instruments or combinations beyond his technical capacity. Although most composers seek a public performance of their works and undoubtedly gain an important satisfaction from it, it is, in my opinion, by no means certain that a desire to communicate a thought or feeling constitutes a primary motivation in the act of musical creation. Consider for a moment the example of Schubert, who was extremely careless in preserving and disposing of his manuscripts. Indeed it is believed that a large number of his compositions have been lost forever[8]. Yet the number of manuscripts which are available to us indicates that he composed a prodigious amount of music, much of which he never even heard. He was, in fact, almost constantly preoccupied with creating. With his and other historical examples in mind, it seems quite possible that the desire to speak to others in music may not be the primary force which drives a composer to create. What he creates is not so much a communication as it is a fantasy*. Actually, he engages in musical fantasy to such an extent that he develops an extraordinary capacity for vivid auditory imagery. He is usually able to dream up a whole orchestra. Even if he is deaf, as was Beethoven, he is able to imagine the most complex harmonies. Some composers have fantasied an entire composition before beginning to notate it. Of course, other composers have preferred to work out pieces at a piano or constantly to correct or revise their musical notations. But all must be capable of a free kind of musical fantasy. The great composer may be a kind of inveterate daydreamer, but fortunately he is sufficiently interested in passing on his work to record it for the rest of us. Perhaps we have a clue here to

* According to Freud[3, 6] all creative activity has its roots in the fantasy life of the individual. To Freud, artistic creation represented an attempt in fantasy to gratify unacceptable unconscious desires. He postulated that in the hands of the artist, the original artistic fantasies underwent various transformations by which they would lose their distinctly personal note, and by which their origins in prohibited unconscious needs would be concealed. Finally they would undergo various elaborations of a purely esthetic nature. Certainly Freud must have been thinking more in terms of an art such as writing than in terms of music, in which he had little interest. If musical composition has its origins in unconscious conflicts, it is certainly not revealing of their nature from its very beginnings in musical fantasy. It is, in fact, difficult to understand the elaboration and transformations of musical ideas into the completed composition along any other than purely esthetic lines. The point is made not so much to contest Freud's theories with respect to creative activity as to affirm the uniqueness of musical creative expression.

the difference between the musician who is primarily a composer and the one who is primarily a performer. Whereas the composer appears to engage primarily in musical fantasies, the performer seems to be communicating by means of music in a more immediate sense. He is interpreting a piece of music for others and is perhaps more primarily concerned with communicating with music than is the creator.

Further theoretical considerations of music as a language suggest that it is not only a nonverbal language but more specifically a preverbal one. One theory holds that receptivity to music is based on stimulation of subcortical centers[9]. Others have believed it to be based on very early instinctual foundations[10-12]. In any event, receptivity to music appears to be at its highest in the early years of life. In addition, it would appear that an infant is receptive to music before he responds to words. It is true that an infant generally learns to speak before he can sing a song, but we must keep in mind the extraordinary interest that parents have in the first words uttered by their children. In this regard the case of Clara Schumann, the daughter of a music pedagogue intent on making a musical prodigy of his child, is interesting. She did not speak until the age of five although she could play the piano at four. She knew the notes of the staff before she had learned her alphabet, and she did become a child prodigy and later a great musician[13]. Turning for a moment to an example of mental illness, it is well known that the so-called autistic child generally displays an extraordinary receptivity for and absorption in music[14]. Whatever the cause of this illness, it appears that these children are fixated at a very early stage of development. It is quite possible, therefore, that music is not only a highly symbolic language but also an archaic and primitive one. All this brings up the natural question of what determines the early choice of music made by the average composer. Without suggesting that the composer is necessarily fixated at or has regressed to an early stage of development, it is possible to speculate that the choice is determined in part by certain features of his personality and its development. At least the matter of so-called talent does not offer the complete explanation.

In the course of examining the musical process, emphasis has been placed upon the abstract and symbolic features of music. It is a matter of interest that some modern artists who have created in other media would appear to have endeavored to translate some of these qualities of music into their own artistic expression. I have reference, for example,

to the abstract quality of much modern art, or to the attempt on the part of Gertrude Stein to divorce the meaning of words from their sound in her poetry. It is also interesting that such works resemble to some extent schizophrenic art productions in their form, although of course not in their value. The writer does not mean to suggest that such artistic movements are rooted in the psychopathology of their creators, or indeed to cast any critical reflections upon these works. The point is mentioned only to emphasize once again the unique quality of musical expression, and to suggest that psychologic factors may be intimately associated with the choice of this activity, whatever these factors may be. But when one attempts to identify the nature of these psychologic factors, whether as determinants, results, or merely associates of the creative activity and choice of medium of expression, one encounters a problem which has as yet not been solved. It is, however, very difficult to deal with the matter of emotional disturbance and musical creativeness without this knowledge. It is for this reason that the musical creative process in its psychologic aspects has been examined so closely, even though it was stated at the outset that there were, in the opinion of the writer, great limitations facing the psychiatrist in such an endeavor. Unfortunately, historical knowledge of the emotional disturbances of great composers is also limited.

Emotional Disturbance and Musical Creativeness

Psychological studies of apparently emotionally disturbed composers are available in the literature [2, 4, 15-17], but they are, for the most part, by way of representing psychologic improvisations; for in most cases relatively little is known about the composer or his illness. Also, since his music fails to reveal his pathology in any specific way because of its abstract quality, examination of the creative product does not aid appreciably in understanding the composer's personality or psychopathology. One must recognize limitations in making diagnostic and dynamic formulations concerning individuals whom one has never examined, on the basis of the relatively scanty material available to us in the case of these creators. The difficulties in understanding the relation between emotional disturbance and musical creativeness are, therefore, very great. It would seem wisest to begin by considering what is known and what can be said about this subject at the present time and to conclude by formulating what approaches might be taken

to expand psychiatric or psychologic knowledge and understanding.

Historical Data and Theoretical Concepts. There are some meaningful observations which emerge in psychologic studies or biographical and autobiographical material. We know of no significant emotional illness in the lives of composers like Bach or even Mozart[2] although this is not to deny their possible existence. On the other hand, a number of great composers were certainly subject to emotional disturbance, in some instances of severe degree. There is a large body of evidence for emotional disturbances in composers of the 19th and early 20th centuries especially. Whether this is a reflection of the growing interest in psychiatry during this period, as well as an increased interest in the creator himself, or whether this indicates that the Romantic composers were a fairly unstable lot, is difficult to say. In any event these people lived recently enough that in some cases it is possible to arrive at a tentative diagnostic impression even with the incomplete material. Such impressions indicate that these composers as a group were not subject to any single kind of illness. For example, Schumann was probably schizophrenic[13]; Mussorgsky was alcoholic[18]; Mahler, who had one lengthy consultation with Freud, was said to have had an obsessional neurosis[19]. As to personality traits in general, if composers do indeed have certain ones in common—notably obsessive-compulsive or schizoid ones —clinical evidence for this is not yet clearly established.

Of special interest are historical observations dealing with the manner in which emotional disturbances affected musical creativeness. In general it would appear that composers oftentimes created under conditions of emotional pressure or symptoms[4, 15, 16]. On the other hand, it is also quite clear that when these disturbances became sufficiently great, creativeness suffered or was even blocked altogether. There are examples of the latter in the cases of Beethoven[17], Hugo Wolf[18], and Schumann[13]. But the larger and more important question is whether unconscious conflicts associated with emotional difficulties in the composer are also associated with his creative drive and productivity. On this point there are controversial opinions. On the one hand, Kubie[7] vigorously asserts that unconscious conflicts and emotional illness distort and impede the creative process. Other writers, as previously indicated, tend to view creativity as an attempt at sublimation of unconscious conflicts. For example, Hitschmann[4], in discussing Brahms and his emotional problems in relation to women, suggests that this composer's

life had to be incomplete "so that his creative life might be whole". However tempting it may be for the writer to engage in a theoretical discussion on this matter, the more important issue, in his opinion, appears to be that present knowledge may not permit any definitive or reliable answer to this crucial question. Indeed, it would seem that the available evidence is not sufficiently conclusive to support or negate either one of these thought-provoking hypotheses; so that the larger and more immediate problem is one of devising scientific approaches which might produce the facts to support the theories. Certain psychiatric approaches will therefore be suggested which might help in some measure to clarify this problem.

Formulation of Various Investigative Approaches. Such studies would be of the nature of clinical research, whether they involved composers who were patients, or those who might participate in a well organized project concerned with creativity, as they have done on occasion before[20, 21]. In addition to applying psychiatric techniques to an understanding of the psychologic meaning of the creative product itself, these studies would be especially concerned with factors at work in the composer's choice of music as a medium of expression and his subsequent development of creative musical ability. In this regard Kubie[7] has expressed the opinion that it would be premature to explore the matter of this choice—that is, why one man paints and another man composes—until one has solved the problem of the choice of neurosis. It would be difficult to take exception to this point of view in the manner in which the problem is stated. Indeed, one could go further and say that when psychiatrists deal with the question of *why* a man develops a particular type of illness, they often end up arguing about the nature of causative factors. But psychiatry has successfully explored the matter of *how* an illness develops, and as such has amassed a wealth of material of psychodynamics without which no modern psychiatrist could function. In the same way, the psychiatrist could examine in the composer *how* the latter came to choose his medium of expression, without attempting at this time to answer the *why* of it. One could, as it were, investigate clinically the psychodynamics of musical activity and creativeness.

Special attention would, therefore, be given to the study of various determining factors including the so-called talent, parental attitudes, and cultural environment, but with special focus upon any psychologic

or psychodynamic factors which might appear to be at work in the choice and development of musical activity. At the same time the psychiatrist would be interested in defining as precisely as possible character traits and normal or pathologic defenses in these individuals, and in investigating the factors involved in the "choice" and development of these. He would be careful to ascertain whether the individual appeared to be primarily a composer or primarily an interpreter, or perhaps equally active in both phases, since the personalities and dynamics of these types of musicians might be very different.

Application of psychiatric techniques might also lead to better understanding of the musical creation itself. It would be helpful to compare the apparent emotional qualities of the music with the mood of the composer, not only in terms of his own statements on the subject, but in terms of clinical observations of his mood during a period of composition. The investigator or therapist could also consider asking composers to free associate to a theme of recent composition with which they are especially preoccupied, much as a patient is asked to free associate to a dream, a conscious fantasy, or to a recurring familiar tune in fantasy[22]. The complexity of the process of musical creation and certain anticipated resistances on the part of the patient would make such an approach difficult. Also the associations would in all likelihood be musical as well as verbal, and a familiarity with the musical language on the part of the psychiatrist might be necessary. But such an approach might in some instances lead to further understanding of the psychologic meaning of the particular creative product, and would have a significance, different from that of statements which composers have made concerning their creative products and creativeness, which are by way of constituting a kind of self-analysis[20, 23, *]. This is a large undertaking for psychiatrists, but it seems doubtful that there will be much progress made in the understanding of the relationship between creativeness and emotional disturbance until psychiatric studies are undertaken which will give due consideration to the type of activity

* In one notable example, a self-analysis by Beethoven of a musical theme suggests that free association as a method of approach could throw some light on the meaning of musical creation. In a letter to a friend, Beethoven described a dream in which he was traveling in the Middle East and finally arrived at Jerusalem. The dream turned to thoughts of the Bible and to Tobias, which was also the name of his friend. At this point a musical theme in the form of a canon, expressing rhythmically the name of his friend, came into the dream. When Beethoven awoke, he was not able to remember the canon. He writes his friend, that on the following day, "I resumed my dream-journey, being on this occasion wide awake, when lo and behold! in accordance with the laws of association of ideas, the same canon flashed across me; so being now awake I held it as fast as Menelaus did Proteus . . ." (from a letter by the composer to Tobias von Haslinger, September 10, 1821, quoted by Shapero, H. in The Musical Mind, in *The Creative Process*, edited by Ghiselin, B., University of California Press. Published as a Mentor Book, New York, 1958).

in which the creator is engaging. This would certainly appear to be so in the case of music, which is fraught with a psychologic significance exclusive to the medium[24]. Also it is my opinion that there continues to be a need for more extensive reporting of clinical data on composers, for in the end one must check one's theories against actual observations.

Psychotherapy and Musical Creativeness. In the meantime, it would seem that whether or not psychotherapy succeeds in the case of an emotionally disturbed composer, there is little if any basis for believing that the process would alter his creativeness in any but a positive direction. It would appear from examination of the musical creative process that whatever the psychologic determinants involved, they have been formed very early in life, some of them quite possibly in infancy. Character traits with which the creative drive may possibly be associated would appear almost certainly to be deeply fixed in these individuals. It would seem most doubtful that a change of deeply ingrained patterns of such early origin could be affected to such an extent as to alter or impede creative drive. In fact psychiatrists are faced with certain limitations in eliminating psychopathologic patterns themselves. During the phase of treatment itself it would be difficult to predict what changes might take place in creative productivity, but eventually the chances are that the alleviation of emotional symptoms and the resolution of certain relatively basic conflicts would have either little effect upon creativeness, or would aid it by freeing the creator from pathologic preoccupations and interferences.

Summary and Conclusions

A review of the literature on creativeness and emotional disturbance suggests that creativeness is perhaps most often dealt with as a kind of general process without sufficient regard to the psychologic significance of the choice and nature of creative expression. Those studies which have focused upon particular kinds of creative activity or creators have tended to deal less frequently with music and composers than with other arts and artists. In this paper the musical creative process has been examined in some detail with respect to its psychologic aspects, with special emphasis upon various features unique to this particular medium of expression. It has been suggested that psychologic factors play a determining role in the choice of music as a medium of creative expression and in the utilization of musical activity primarily

for creative rather than for performing purposes. The nature of such factors remains, however, essentially unknown. It would seem that such knowledge, in view of certain unique psychologic features of musical expression, would be crucial to an understanding of the relation between musical creativeness and emotional disturbance. Historical data and retrospect psychologic studies of deceased composers suggest that frank emotional disorder occurred in some but not all of these creators. If such disturbance could not be viewed as a prerequisite to musical creativeness, it apparently was not a deterrent except in cases in which it became relatively extreme. Whereas there is evidence to suggest that musical creativeness may be a function of the fantasy life of the composer, the crucial question as to whether such activity represents an attempt at resolution of unconscious conflicts, or whether it takes place independently of and can be impeded by such conflicts, would seem to be difficult to answer in light of present knowledge. At this time the need seems to be less for further theoretical speculation than for more extensive and reliable clinical data. Various approaches for clinical psychiatric investigation have been suggested as a possible means for clarifying the problem to some extent. Pending such investigations, it would appear that fears that psychotherapy might impede creative activity are essentially without clinical basis. If anything, such treatment could be expected to enhance the creative productivity of the composer.

Discussion

Douglas Moore, Mus. D.,—*MacDowell Professor of Music, Columbia University, New York, N. Y.*

With practically all of Dr. Sherwin's paper I find myself in substantial agreement. Dr. Sherwin, himself an excellent musician, experienced as both performer and composer, speaks with authority both as psychiatrist and musician.

The point which he raises in the first paragraph and which he restates in his conclusion that psychotherapists need not be fearful of injuring creativity by treatment is clearly indicated by my experience with composers. Composition is an activity which requires great energy and mental vigor. Impairment by illness will lessen and may kill it. If it were true that psychotherapy reshuffled the personality to the extent of weakening the creative drive and substituting other objectives, there might be danger. I can merely state that the will to create, once manifested and implemented with achievement, is so powerful that I doubt if such substitution could be made. I have known several composers who have been subjected to therapy and have never seen a case where the creative drive slackened.

The use of the term *fantasy* to describe the process of composition seems dangerous to me. Actually the imaginative structure which the composer builds is

made with very real components, tone and rhythm. Granted that the language is non-verbal (also the case in architecture, painting and sculpture), the process of thought is far removed from what is known as *daydreaming*. The composer works with very real musical ideas and subjects his material to severe disciplines of tradition and practice. Musical ideas may be manufactured by an experienced musician but by common belief, the mysterious factor of inspiration is present in works of lasting value and appeal. The greatest ideas, which admittedly may originate in the fancy, are abortive unless coupled with a high degree of technical manipulation, and this process is an intellectual skill of the highest and most demanding order.

The difference between composer and performer is a gulf often bridged but there is a wide difference in loyalty. To the performer, the written note is (or should be) sacred. He devotes his effort primarily to the realization of the composer's intention even in the smallest detail. The composer, even in performing his own music, can never be so faithful. Primarily an inventor and realizing the countless decisions that have gone into the creation of the work, he cannot but think of alternatives which might have been better. In my own case, starting out with the study of the piano, I found improvising much more attractive than practicing and a constant interference with progress as a performer. I agree with Dr. Sherwin that the creative gift manifests itself at an early age. Every well trained musician must learn the composing skill. Such performers who discover later that they are composers usually lack the drive that is necessary to succeed.

As to the motivation in choice of the career by the composer, I believe that the individual early in life falls under the spell of music, finds his greatest happiness in associating with it, and is carried through the arduous labors of acquiring a technique by a combination of the factors of environment and character. As to the mood in which he composes, he cannot wait as some artists do for high spirits or inspiration. His is a job of such magnitude in dealing with such large forms as symphony and opera, that he must work long hours every day, regardless of how he feels. A good day brings happiness, a bad one something bordering on despair. Encouragement and success will probably increase his output, but I have known composers whose drive and belief in themselves surmounted a lifetime of failure.

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In this discussion I wish to emphasize and review some of Dr. Sherwin's points. One must fully recognize that we are studying the created product and not the creative process which, for example, may have occurred at periods of inner peace or turmoil. The final product is not necessarily the direct expression of these varied emotions, because the creation may fill a need on the part of the creator or express a longing for something different. Creative art is the expression of the individuality of a living person and not a communication. In music, an additional difficulty in the evaluation of the creative process exists in the fact that the musician who plays the composition expresses his individuality in his performance.

Studies of the creative processes of a musician are necessarily made after the work has reached some point of completion and cannot be undertaken during the actual creating. Studies in psychiatric and psychologic literature do not do justice to the dynamic flow of the creative process where no situation, within the person

or outside him, can be the same from one period of time to another. This difficulty of human study presents itself in any psychologic observation and investigation, but seems insurmountable in artistic creation. It is unacceptable to apply psychologic scrutiny, if one wishes to present more than an essay, to the work and life of an artist whom one has not examined and studied for the same reasons. Psychiatric diagnoses in such cases must be rejected.

The concept of unconscious and the thoughts referring to sublimation and creative processes by Kubie and Fenichel are based on psychoanalytic theory and experience. If we apply Leibnitz' concept of unconscious or the current concepts of existentialism or Daseinpsychology, one might argue differently. To offer an example, Nietzsche's criticism of Wagner must be reviewed from the broad point of view as to how much the technical refinement interferes with true expression; that is, the true creative process, and what is the optimal degree of expression and form.

REFERENCES

1. Arlow, J. A. Panel report on Sublimation, *J. Amer. Psychoanal. Assoc. 3*:515-27, 1955.
2. Esman, A. H. Mozart: A study in genius, *Psychoanal. Quart. 20*:603-12, 1951.
3. Fraiberg, L. Freud's writings on art, *Int. J. Psycho-Anal. 37*:82-96, 1956.
4. Hitschman, E. Brahms and women, in *Great men; psychoanalytic studies.* New York, International Universities Press, Inc., 1956.
5. Lee, H. B. On the esthetic states of the mind, *Psychiatry 10*:281-306, 1947.
6. Sterba, R. The problem of art in Freud's writings, *Psychoanal. Quart. 9*: 256-68, 1940.
7. Kubie, L. S. *Neurotic distortion of the creative process.* Lawrence, University of Kansas Press, 1958.
8. Lang, P. H. *Music in western civilization.* New York, W. W. Norton & Company, Inc., 1941.
9. Altschuler, I. M. Four years' experience with music as a therapeutic agent at Eloise Hospital, *Amer. J. Psychiat. 100*:792-94, 1944.
10. Coriat, I. H. Some aspects of a psychoanalytic interpretation of music, *Psychoanal. Rev. 32*:408-18, 1945.
11. Kohut, H. and Levarie, S. On the enjoyment of listening to music, *Psychoanal. Quart. 19*:64-87, 1950.
12. Sterba, R. Toward the problem of the musical process, *Psychoanal. Rev. 33*: 37-43, 1946.
13. Burk, J. N. *Clara Schumann: a romantic biography.* New York, Random House, 1940.
14. Sherwin, A. C. Reactions to music of autistic (schizophrenic) children, *Amer. J. Psychiat. 109*:823-31, 1953.
15. Hitschmann, E. Franz Schubert's grief and love, *Amer. Imago 7*:67-75, 1950.
16. Squires, P. C. Peter Ilich Tschaikowsky: a psychological sketch, *Psychoanal. Rev. 28*:445-65, 1941.
17. Sterba, R. and E. Beethoven and his nephew, *Int. J. Psycho-Anal. 33*:470-78, 1952.
18. *Grove's Dictionary of music and musicians,* 5th ed. Eric Blom, editor. New York, St. Martin's Press, 1954.
19. Jones, E. *The life and work of Sigmund Freud,* Vol. II. New York, Basic Books, Inc., 1955, pp. 79-80.
20. Whittaker, W. G., Hutchison, W. O. and Pickford, R. W. Symposium on the psychology of music and painting, *Brit. J. Pyschol. 33*:40-57, 1943.
21. Willmann, R. R. An experimental investigation of the creative process in music, *Psychol. Monogr. 57*:1-76, 1944.
22. Sherwin, A. C. A consideration of the therapeutic use of music in psychiatric illness, *J. Nerv. Ment. Dis. 127*:84-90, 1958.
23. Mozart, W. A. A letter quoted in *The creative process,* B. Ghiselin, editor. University of California Press. Published as a Mentor Book, New York, 1958.
24. Kohut, H. Observations on the psychological functions of music, *J. Amer. Psychoanal. Assoc. 5*:389-407, 1957.

RESEARCH OR STAGNATION*

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RESEARCH in a broad sense is our subject. Besides believing only in the practical value of scientific investigation, we should occasionally pause to consider the importance of research to our twentieth century way of life, and examine our attitude toward scientific study with a detachment which permits perspective. In so doing, we may see how far-reaching are the effects of research, how they concern all of us, and we come to realize how research cannot be divorced from good teaching or from good clinical practice. At the same time we become aware that "stagnation" may not be a term to be applied only to science, but might be equally descriptive of the state of an individual.

I. *Research drives:*

There are two basic reasons for conducting research: first, the practical – to find useful things – and second, the more fundamental, man's curiosity about his environment. In the practical, a need is seen, and a solution sought. However, when curiosity is the motivation, the sequence changes. As a result of curiosity an understanding may be gained, and occasionally an application of such knowledge is made.

Both systems are inefficient. For example, in England during the war-caused food shortage, great efforts were made to improve such things as milk production, a long-term goal to be attacked by the study of genetics and hormonal influence which eventually yielded results. However, it is obvious that such objectives cannot be obtained quickly, when the need is greatest, but should be anticipated and patiently sought long in advance.

On the other hand, the research program stimulated by intellectual

* Presented at a meeting of the Section on Ophthalmology of The New York Academy of Medicine, February 16, 1959.

curiosity is often criticized as diffuse, with no obviously practical goal. The objection to this criticism is simply that no one can tell what will be useful, and how, or when. It is a shallow and superficial attitude toward what is essentially an intellectual pursuit, such an attitude as that of those who found no beauty or "value" in the paintings of Gaugin, for instance.

It is most impressive to read how many common and highly useful techniques have been invented and developed as mere adjuncts to fundamental studies, which in themselves had no immediate practical application. For example, Joseph Plateau invented the stroboscope[1] only to satisfy his curiosity about the complicated motion of insect wings in flight. Work directed at one objective frequently provides essential data for achieving another. Atomic fission was developed for military purposes and promised vast sources of economical power for peaceful civilian use, the realization of which is still far off, whereas a great use of atomic products has already been found in medicine, although this was not originally anticipated. Similarly, in reading the discussion of aqueous humor dynamics in Davson's[2] book *The Physiology of the Ocular and Cerebrospinal Fluids*, one finds that he explains the fundamental physiology involved by drawing analogies with basic data obtained from experiments on Chara, a large-celled alga.

Some years ago W. H. Lewis[3] discovered the process of pinocytosis during his studies of fibroblasts in tissue culture, a process the general importance of which is just now being realized. In the Third Proceedings of the Macy Foundation *Symposium on Glaucoma* you will read how Professor Barany presented strong arguments for involving this process in the secretion of aqueous humor. Hence, one must conclude that apparently "inefficient" research, having its genesis in scientific curiosity, frequently sparks the greatest and most productive investigative drives. H. L. Mencken accurately commented that mere curiosity is the strongest drive in research, stating that the "prototype [of the scientist] is not the liberator releasing slaves, the good samaritan lifting up the fallen, but a dog sniffing tremendously at an infinite series of rat holes"[4]. Even if this be true, one need not wait complacently until a solution to a practical need is found by chance. One can and should direct attention toward such problems as attractive fields for investigation, rather than await the results of completely aimless "sniffing". In medicine no one is in a better position to do this than is the clinician.

II. *In what context should research be regarded?*

Should research be regarded 1) as a business, 2) as a service (such as legal, medical, educational, ministerial) or 3) does it belong with philosophy and the arts? Without question, it is in this latter group that basic research finds its place. Norman Campbell[5], the British scientist, writing on the philosophy of science, found that: "Nothing could be more absurd than the attempt to distinguish between science and art. Science is the noblest of the arts and men of science the most artistic of all artists. For science, like art, seeks to attain esthetic satisfaction through the perceptions of the senses; and science, like art, is limited by the impositions of the material world on which it works." He went on to state that, although most scientists cannot receive acclaim, most musicians did not compose a Fifth Symphony—yet each individual may have his moment of creative joy and stand for that moment "with the great ones". This is probably the greatest reward that artists and scientists alike ever receive.

If research workers are to be regarded in the same category as artists, are they, in general, professional scientists or avocational? Classically, most of them have been avocational, as have artists; their scientific pursuit has been coupled with some other occupation by which they earn their living, such as teaching or the practice of medicine. Clearly, there should be no distinction made between clinical and laboratory research, although that distinction is often made, and frequently by the clinician. Because of variability of the subject and limitations imposed on the actions of the investigator, clinical research is much more difficult than that done in the laboratory. Greater effort is required to discover suitable means of investigation, and particularly to analyze results critically. Clinical investigation has tended more toward the descriptive or natural history type of study but must not be confined to it. Addison, in the middle of the last century, described adrenal insufficiency, and undoubtedly today there is the feeling that such far-reaching clinical opportunities no longer exist. However, equivalent opportunities are still present. Since more basic information and better physical tools are now available, more subtle clinical problems can be attacked. I have been most interested in exophthalmos, and have long felt that laboratory investigations of this subject are grossly handicapped by lack of information on the orbital pathology of clinical

cases. Although exophthalmos has excited interest for well over 100 years, it was only a few years ago that Dr. Rundle and his colleagues reported the first quantitative analysis of the changes occurring in the entire orbit of a case of progressive or infiltrative exophthalmos[6]. We have many reports on the pathology of small biopsy specimens, but in only this case was a report on the complete orbit made. It does not detract from Rundle's paper to say that more such cases would be most valuable, and that an even more complete investigation could be accomplished.

An example of excellent clinical research, which is both important and familiar to you, illustrates well how the correlation of various isolated bits of basic research have aided in avoiding stagnation in one field, and how the keen clinician can, through research, avoid stagnation in his field and, incidentally, in himself. The Diamox story has glamour. The sulfonamides were discovered in 1908 and the original interest was in the dye industry. In 1917 it was found that these compounds destroyed bacteria *in vitro*. Their protective properties against bacteria *in vivo* were reported in 1932[7]. Naturally, the chemists were interested in which configuration of the sulfonamide molecule was responsible for its bactericidal action. They found that acetylation greatly reduced that desirable action, but enhanced its effect as a carbonic anhydrase inhibitor, providing a drug useful in promoting diuresis. Completely unrelated to these studies was the work of Kronfeld[8] demonstrating an excess of bicarbonate in the aqueous humor. In 1944 Friedenwald[9] pieced together many bits of evidence, constructing a theory which would explain the formation of aqueous humor and in which a consideration of the bicarbonate played an important role. Kinsey[10] provided strong supporting data by showing that the bicarbonate ion was in greatest excess in the posterior chamber where the aqueous humor was formed —a contribution which was part of his "sniffing" program about the general field of aqueous dynamics. In 1951 Wistrand[11], in Upsala, found an enzyme, carbonic anhydrase, in the anterior uveal tract—an enzyme which would promote the formation of a bicarbonate excess in aqueous humor. Now came a period of stagnation, until alert investigative minds appreciated these facts. The necessary facilities and information were available to all. Suddenly, in 1954, Becker[12] in St. Louis, Grant in Boston[13], and Breinin in New York[14] independently reported that they had put this information together and applied it in the treatment

of glaucoma, with the results we all know.

This is perhaps an outstanding example of how research should and can be coupled with clinical practice. Just as important, however, if less newsworthy, is each diagnosis, which is, I think, also a research problem. An inquisitive, research-oriented mind regularly directed at biological problems is the most suited to and, therefore, the most successful in advancing practical medicine. Possibly 80 per cent of diagnoses and treatment could be made and prescribed by an advanced resident in ophthalmology. Very possibly also, there are a few per cent of cases for which no diagnosis can be made at this time, leaving about 15 per cent which only the trained investigative mind can solve. Each of these is a real research problem.

III. *Effect of research on society:*

We have discussed the drives responsible for research; the fact that one cannot predict what results will be immediately useful; that all of us are engaged in some form of research, whether we claim to be or not; and also, that opportunities for research in clinical medicine are far greater than is often realized. What is the effect of all of this investigative effort on our society?

The general direction which the development of our society takes is unquestionably determined by many subtle and diverse factors. It has been asserted, for example, that the character of the European social scene at the close of the nineteenth century was unmistakably influenced by Balzac, whose novels actually created or emphasized many of the attitudes which existed at that time, rather than merely depicting them. For the moment, disregarding the obvious influence of the physical sciences on our way of life, let us consider instead the impact of biology. Research efforts of the past century have resulted, among other things, in lengthening the life span, which affects and will have an increasing effect in the future upon 1) living conditions, 2) retirement and social security, and 3) insurance and banking. The increased numbers of aged individuals in the population will certainly express their point of view in new laws. It is not the politician nor the financier who creates the social order; they serve it. This effect of research on society itself creates the necessity of further research, because new problems arise as the result of the solution of others.

Increasing with the world population and the life span are ophthalmic problems, mainly among degenerative diseases. These are serious problems in our society. Among the earth's inhabitants, there are vast numbers of the blind—numerically equal to the total population of Canada[15]. Enormous numbers, especially in the Orient and Near East, have good retinae behind scarred and opaque corneae. The surgical technique of corneal transplantation has been beautifully perfected, but development of an immune reaction to the graft, in all too many cases, cancels the excellence of the surgery. The problem of tissue immunity remains a major one to be solved through research. In 1903 Uhlenhuth[16] demonstrated that an immunity could be developed to a homologous organ, the lens. His study was an early one in this field to which some of today's most pressing medical problems appear to belong. This area of research, academic 56 years ago, is practical today.

Excluding infectious diseases and accidents, both of which we can now control to a great degree, congenital, hereditary and degenerative diseases are the main causes of blindness. The proportion of these cases will continue to increase, and we must not reach stagnation at this point. Research will continue, of course, but it requires effort and support of both laboratory worker and clinician, and especially the enthusiastic support of the latter. In the end all share in the pride of accomplishment. We must do this because it is practical to help our fellows in society; because in this way we advance our profession, and in our profession; because it is paramount to our satisfaction as creative workers, and because, as we all know, the finest physicians and teachers are those who remain at heart interested students.

Finally, we should enter actively into research, and insure that it is supported, for the attractive reason given by Duke-Elder[15], who said research is "worthwhile because the finding out of new things, of being alive, of being a spearhead in world progress, is always great fun".

REFERENCES

1. Quoted from Hocking, B. Insect flight, *Sci. Amer. 199:6*:92-98, 1958.
2. Davson, H. *The physiology of the ocular and cerebrospinal fluids*. Boston, Little, Brown & Co., 1956.
3. Lewis, W. H. Pinocytosis, *Bull. Johns Hopk. Hosp. 49*:17-27, 1931.
4. Quoted from Pitzer, Kenneth S. Role of the university in basic research, *Science 121*:789-92, 1955.
5. Campbell, Norman Robert. Science, imagination, and art, *Science 125*:803-06, 1957.
6. Rundle, F. F., Finlay-Jones, L. R. and Noad, K. B. Malignant exophthalmos: a quantitative analysis of the orbital

tissues, *Aust. Ann. Med. 2*:128-85, 1953.

7. Galdston, I. *Behind the sulfa drugs.* New York and London, D. Appleton-Century Co., Inc., 1943.
8. Kronfeld, P. Der Kohlensäuregehalt des Kammerwassers, *v. Graefe's Arch. Ophthal. 118*:606-32, 1927.
9. Friedenwald, J. S. Dynamic factors in formation and reabsorption of aqueous humour, *Brit. J. Ophthal. 28*:503-10, 1944.
10. Kinsey, V. E. Comparative chemistry of aqueous humor in posterior and anterior chambers of rabbit eye, *A.M.A. Arch. Ophthal. 50*:401-17, 1953.
11. Wistrand, P. J. Carbonic anhydrase in the anterior uvea of the rabbit, *Acta physiol. scand. 24*:144-48, 1951.
12. Becker, B. Decrease in intraocular pressure in man by a carbonic anhydrase inhibitor, Diamox, *Amer. J. Ophthal. 37*: 13-15, 1954.
13. Grant, W. M. and Trotter, R. R. Diamox (acetazoleamide) in treatment of glaucoma, *A.M.A. Arch. Ophthal. 51*: 735-39, 1954.
14. Breinin, G. M., and Görtz, H. Carbonic anhydrase inhibitor acetazoleamide (Diamox), *A.M.A. Arch. Ophthal. 52*: 333-48, 1954.
15. Duke-Elder, W. S. Research and the prevention of blindness, *Ophthal. Res. Inst. Australia, Inc.*, no. 1, 1957.
16. Uhlenhuth, P. *Zur Lehre von der Unterscheidung verschiedener Eiweissarten mit Hilfe spezifischer Sera.* In *R. Koch Festschrift*, Jena, G. Fisher, 1903, p. 49.

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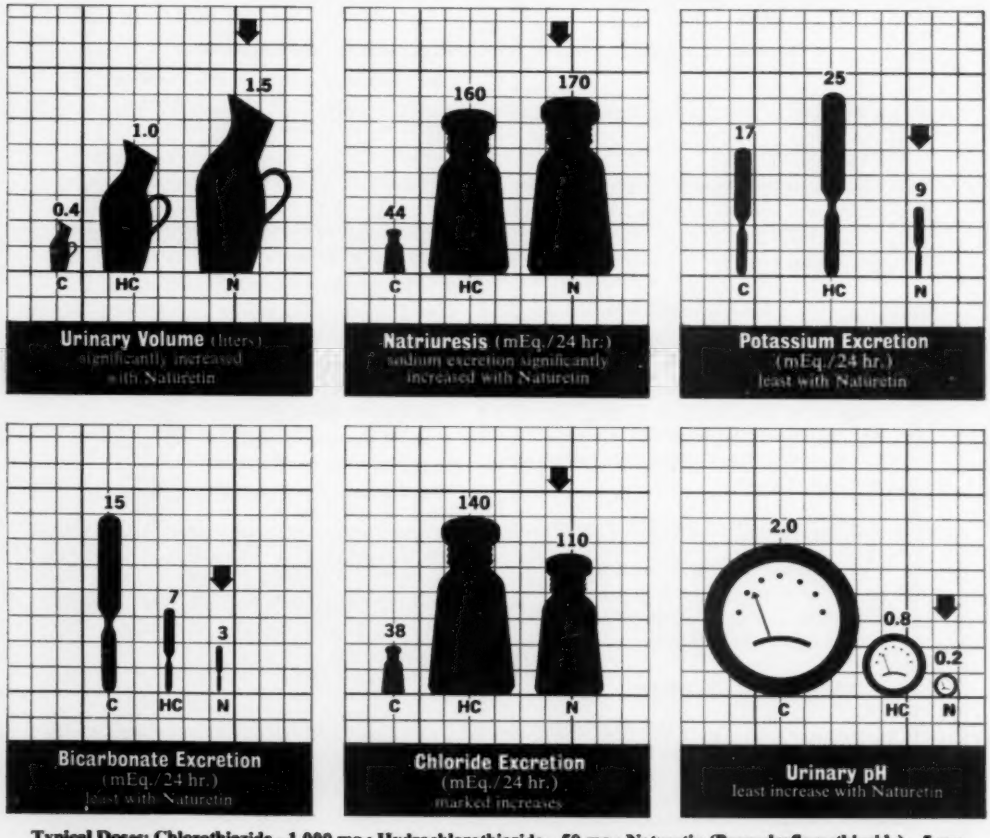
Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin[1]



Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydroflumethiazide)—5 mg.

1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.

A single 5 mg. tablet once a day provides all these advantages[2]

- prolonged action — in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage — more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity — few side effects — low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

Naturetin —*Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

Contraindications: none, except in complete renal shutdown.

Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

Naturetin —*Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

Naturetin —*Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

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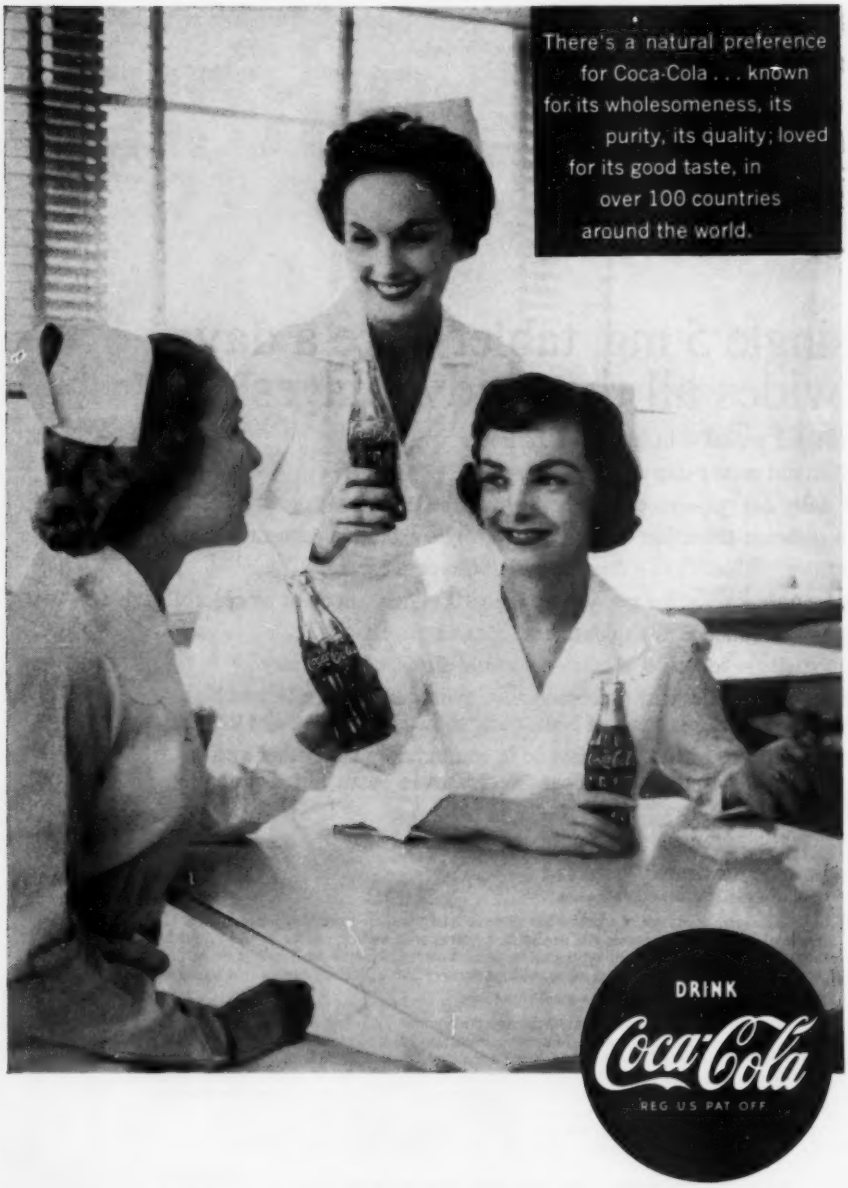

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Dosage

'MIGRAL' should be taken immediately at the start of a migraine attack, and the effective dosage should be determined on an individual basis. When the total dosage necessary to stop an attack has been determined, that amount should be taken as initial dosage in subsequent attacks.

In general, 2 to 4 'MIGRAL' tablets taken at the first sign of an attack will terminate a headache by preventing progression to the vasodilation stage. If treatment is not started sufficiently early to achieve this result, an additional 1 or 2 tablets should be administered every half hour until the patient is relieved, or until a total dosage of 6 tablets has been taken.

Caution

It is recommended that not more than 6 tablets be taken during a single attack, nor more than 10 tablets per week.

Each sugar-coated 'MIGRAL' tablet provides:

Ergotamine Tartrate	1 mg.
'Marezine'® brand Cyclizine Hydrochloride	25 mg.
Caffeine	50 mg.

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For complete information on dosage forms, dosage schedules and precautions, consult literature available on request.

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